Protonix FDA Advisory Committee Briefing Document

PROTONIX® Tablet

PROTONIX® I.V.

Pantoprazole Granules

Pantoprazole sodium Delayed-Release Tablets: NDA 20-987

Pantoprazole sodium for Injection: NDA 20-988

Pantoprazole Granules: NDA 22-020

Results of Pantoprazole Studies in Pediatric Patients One Month Through 11 Months With Gastroesophageal Reflux Disease (GERD)

Gastrointestinal Drugs Advisory Committee Meeting – 05 November 2010

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1.0 OVERVIEW

Gastroesophageal reflux (GER) occurs commonly in infants and is considered to be a normal physiologic process. Studies of normal infants have demonstrated episodes of reflux as frequent as 73 times per day,[1] and GER-associated vomiting has been reported to occur in as many as 67% of infants during the fourth month of life.[2] For over 98% of infants, GER resolves by 12 to 15 months of age. Among infants who have significant regurgitation lasting longer than 90 days, some may experience symptoms of GERD a decade later.[3] Whereas GER is common in infants, gastroesophageal reflux disease (GERD), defined as reflux that is associated with pathologic signs and symptoms, is uncommon. GERD may be a significant source of morbidity in infants, manifesting as anorexia, dysphagia, arching of the back during feedings, irritability, hematemesis, anemia and failure to thrive.[4] GERD may also predispose some infants to chronic respiratory disease including cough, asthma and recurrent pneumonia.

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) Guidelines for Evaluation of Gastroesophageal Reflux in Infants and Children that were issued in 2001 included treatment recommendations for both nonpharmacologic therapy, such as thickened infant formula and attention to positioning, as well as pharmacologic treatment.[4] These guidelines did not recommend chronic use of antacids in infants due to concerns about safety of aluminum and lack of data regarding magnesium and calcium-containing antacids; however, they recommended a trial of histamine-2 receptor antagonists (H_2RAs) or proton-pump inhibitors (PPIs). At the time, no data from large randomized clinical trials of PPIs in infants had been published, but limited data from small clinical trials of PPIs in full-term and preterm infants had demonstrated efficacy and safety in the treatment of GERD.[5,6,7] To gain more information about PPIs in infants, in December 2001, the United States Food and Drug Administration (US FDA) requested Wyeth (acquired by Pfizer Inc. in October 2009), along with other PPI Sponsors to conduct an efficacy study and a pharmacodynamic study in infants within a battery of pediatric studies in a Pediatric Written Request (PWR).[8,9]

Pantoprazole (Protonix®; Wyeth Pharmaceuticals [now a wholly owned subsidiary of Pfizer Inc.]) is a PPI that has been shown to be safe and effective in the treatment of erosive GERD in adults and children in randomized controlled clinical trials.[10,11,12,13,14] Pantoprazole delayed-release granules for oral suspension was originally developed in response to the PWR from the FDA (31 December 2001) for an age-appropriate formulation for the study of pantoprazole sodium in clinical trials in infants and children.

The purpose of this Gastrointestinal Drugs Advisory Committee Meeting is to discuss results from the clinical trials conducted in infants 1 through 11 months of age in response to the Pediatric Written Requests for proton pump inhibitors (PPIs). The goal of the meeting is to provide a forum for discussion of the challenges as well as lessons learned from the infant GERD studies between the Agency, Sponsors, and Academic community.

The purpose of this document is to provide:

- A brief review of the studies conducted with Protonix in pediatric patients 1 through 11 months of age
- An overview of the symptoms assessment tools (development of GSQ-I and e-Diary) developed for the studies in infants
- Key results from each study
- Challenges in performing studies in infants
- Discussion of the limitations and learning from the infant GERD efficacy study
    - Limitations of the study design
    - Possible reasons for lack of relapse
    - Suggestions for future research

Overall 254 patients 1 through 11 months of age with symptomatic GERD were treated from 5 days to 8 weeks in 3 studies (3001B3-333-WW, 3001B3-335-WW, and 3001B3-329-WW) which were conducted between 01 February 2006 and 25 March 2008. These studies were conducted in response to a formal Pediatric Written Request (PWR) issued on 31 December 2001. The major study design components, including patient population, and main inclusion criteria were set forth by the FDA as PWR Study 2 (Pharmacokinetic, Pharmacodynamic and Safety in Pediatric Patients 1 to 11 Months of Age) and Study 3 (Efficacy and safety Evaluation of Pediatric Patients 1 to 11 Months of Age). In the battery of tests were pharmacokinetic (PK), pharmacodynamic (PD) and efficacy studies. Details of the study designs in the PWR underwent several updates since Dec 2001, and Wyeth Pharmaceuticals received the final version of the request for pantoprazole pediatric studies from the FDA in 2007 (see Section 2.0).

The pharmacodynamic study (3001B3-333-WW, 24-hour pH-metry) in infants 1 through 11 months, indicated that the higher pantoprazole dose (1.2 mg/kg equivalent) was effective in significantly raising the mean gastric pH and percentage of time that gastric pH was > 4. The 1.2-mg/kg dose also provided statistically significant decreases in the AUC and the normalized

AUC of the esophageal H^+ activity, a more sensitive measure of acid exposure, from baseline to steady state. The results of this study supported the choice of the 1.2-mg/kg daily dose used in study 3001B3-329-WW, which was conducted in infants aged 1 month through 11 months.

The results of study 3001B3-329-WW showed that pantoprazole sodium 1.2 mg/kg equivalent reduced symptoms of GERD in infants 1 through 11 months with a clinical diagnosis of GERD although no difference in withdrawal rates from placebo was demonstrated in this treatment-withdrawal study. After 4 weeks of treatment, the majority of patients treated with placebo along with conservative treatment and rescue antacids continued to do well and were indistinguishable from those who continued treatment with pantoprazole 1.2 mg/kg equivalent.

There are numerous challenges in undertaking studies in infants. The PPI Sponsors started these studies after the studies in older children due to the extensive preparatory work required, such as neonatal toxicology, formulation development and gaining regulatory agreement on study design and requirements. Conduct of the studies was difficult due to the ethical concerns regarding studying a fragile patient population. Finally, it was difficult to find qualified sites and investigators in the US, leading to the need for worldwide studies.

The failure of the clinical trials of PPIs in infants to demonstrate the primary efficacy endpoints was unexpected. However, the lack of ability to firmly make a diagnosis and exclude diseases with overlapping symptoms was a significant handicap. Selection of symptoms and development of novel symptom tools for caregiver reporting was also difficult and added additional complexity. Future studies of PPIs in infants need to focus on selecting a population with more severe disease who are most likely to benefit from PPI therapy. Excluding patients who respond to conservative therapy and have a normal reflux index may help define the population with acid-related symptoms. Additional refinement of symptom tools in this population is needed. A parallel-design comparator study may have significant advantages over a treatment-withdrawal design due to the impact of maturation on symptoms.

2.0 WRITTEN REQUEST FOR INFANTS 1 TO 12 MONTHS WITH GERD

This document provides a background and overview of the clinical studies conducted in infants ages 1 through 11 months that were in response to the pantoprazole PWR letter issued by the US Food and Drug Administration (FDA) on 31 December 2001 for PROTONIX® (pantoprazole sodium) Delayed-Release Tablets (New Drug Application [NDA] 20-987) and PROTONIX® I.V. (pantoprazole sodium) for Injection (NDA 20-988). The pantoprazole PWR

was originally issued on 31 December 2001 and the most recent amendment was on 17 May 2007, with a time frame of 31 December 2008 for reporting the studies.

Pantoprazole sodium sesquihydrate, 5 (difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole, monosodium salt, sesquihydrate, which may also be referred to as pantoprazole or pantoprazole sodium, is a substituted benzimidazole derivative. Pantoprazole is a potent, acid-activated, irreversible inhibitor of the H^+/K^+-ATPase of parietal cells and produces prolonged suppression of gastric acid secretion. Intravenous (IV) and oral formulations of PROTONIX® (pantoprazole sodium) have been marketed worldwide. The use of pantoprazole sodium delayed-release tablets for short-term treatment (up to 8 weeks) in the healing and symptomatic relief of EE (NDA 20-987) was approved in the United States on 02 February 2000, its use for maintenance of healing of EE and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with GERD (NDA 20-987/S-001) was approved on 12 June 2001, and its use for pathological hypersecretory conditions including ZES (NDA 20-987/S-007) was approved on 19 April 2002.

The use of IV pantoprazole (NDA No. 20-988) for short-term treatment (7 to 10 days) of patients having gastroesophageal reflux disease (GERD) with a history of erosive esophagitis (EE), as an alternative to oral therapy in patients who are unable to continue taking oral pantoprazole, was approved on 22 Mar 2001, and its use for the treatment of pathological hypersecretory conditions associated with Zollinger-Ellison syndrome (ZES) was approved on 19 Oct 2001. Intravenous pantoprazole received approval for short-term treatment (7 to 10 days) of patients having GERD with a history of EE in 2009.

The use of pantoprazole for delayed-release oral suspension for the short-term treatment of EE associated with GERD, maintenance of healing of EE, and pathological hypersecretory conditions including ZES (NDA 22-020) was approved in the United States on 14 November 2007.

An oral formulation of pantoprazole sodium delayed-release granules was originally developed in response to the Protonix PWR from the FDA (31 December 2001) for an age-appropriate formulation for the studies of pantoprazole sodium in clinical trials in infants and children. In response to FDA's request, Wyeth Pharmaceuticals developed this granule formulation of pantoprazole for use in patients who are unable to swallow tablets; however, these formulations could not be scaled for commercial manufacturing. There were 2 modes of administration for

pantoprazole sodium for delayed-release granules to facilitate oral ingestion in infants and children:

a) sprinkled on a teaspoon of applesauce or apple juice
b) suspended with an inert powder blend in water and administered via an oral dispenser.

Pharmacokinetic (PK) and pharmacodynamic (PD) evaluations in infants 1 through 11 months of age were requested as a part of the PROTONIX® PWR. Wyeth Pharmaceuticals, conducted appropriate pediatric studies in infants 1 through 11 months of age using pantoprazole sodium delayed-release granules to satisfy the requirements specified in the FDA's PWR, dated 17 May 2007. These studies are briefly described below.

1. PK, PD, and safety study in infants ages 1 through 11 months (study 3001B3-333-WW) in response to the PK/PD components of the PWR.
2. Supportive safety and tolerability of pantoprazole granules in infants less than 12 months of age with presumed GERD (study 3001B3-335-WW). This was an open-label extension study for the patients who previously enrolled in studies 3001B3-333-WW and 3001B3-331-WW (PK/PD and safety in premature infants and neonates).
3. Efficacy and safety evaluation of pediatric patients 1 through 11 months of age with symptomatic or endoscopically proven gastroesophageal reflux disease (GERD) (study 3001B3-329-WW) in response to the efficacy and safety component of PWR.

The study designs including the number of patients in each study for the 3 studies in infants 1 through 11 months old are presented briefly in Table 2-1; details of studies 3001B3-333-WW and 3001B3-335-WW are described in Section 3.0. Development of symptom assessment tools for infants 1 to 11 months is presented in Section 4.0 and the results of study 3001B3-329-WW is presented in Section 5.0 following by discussion of infant studies prospective in 2010 (Section 6.0) and the overall discussion and conclusion in Section 7.0.

Table 2-1: Summary of Studies in Infants 1 to 12 Months

Wyeth Pharmaceuticals Study Number/CSR/Study Dates	Study Description	Formulation Duration of Treatment	Number of Patients[a]	Age of Patients
Pharmacokinetic, Pharmacodynamic, and Safety Study				
3001B3-333-WW CSR-70840 01 Feb 2006 to 29 Jan 2008	A Multicenter, Randomized, Open-Label, Single- and Multiple-Dose Study of the Pharmacokinetics and Pharmacodynamics of 2 Dose Levels of Pantoprazole Sodium Enteric-Coated Spheroid Suspension in Infants Aged 1 Through 11 Months.	Granules/7-days including 5 consecutive days	67	1 through 11 months with presumed GERD
Supportive Safety Study				
3001B3-335-WW CSR-70842 14 Mar 2006 to 25 Mar 2008	Open-label safety extension study, with patients assigned to 0.6 mg/kg or 1.2 mg/kg based on clinical response or pH-metry data in preceding studies (331 and 333).	Granules, oral, once daily were dispensed by weight group. Treated for 6 weeks.	58[c] (These patients rolled over from studies 331 or 333).	Infants < 12 months with presumed GERD
Efficacy and Safety Evaluation				
3001B3-329-WW CSR-70839 28 Sep 2006 to 26 Nov 2007	Phase 3, outpatient, randomized, double-blind, multi-dose; placebo-controlled withdrawal study of efficacy and safety of pantoprazole granules in male or female infants. An e-Diary symptom questionnaire based on the modified GSQ-I was completed daily to assess the frequency of GERD symptoms. A 4-week open-label treatment run-in phase, followed by a 4-week placebo-controlled withdrawal phase. Efficacy is based upon the difference in withdrawal rates during the 4-week placebo-controlled withdrawal period.	Granules, or matching placebo, oral, once daily were dispensed by weight group. 8 weeks	129 patients in safety OL Phase = 128 patients DB Phase = 108 patients	1 through 11 months with symptomatic GERD

a. Safety population.
b. Administration of granules by sprinkling on a teaspoon of applesauce or apple juice for ages 1 to < 6 years.
c. These patients rolled over from studies 331 or 333 and were counted only once in the safety database.

Study 331 was conducted in term and post-term infants within the neonatal period (≤ 28 days postnatal age).

Abbreviations: CSR = clinical study report; FDA = U.S. Food and Drug Administration; GERD = gastroesophageal reflux disease; PD = pharmacodynamic; PK = pharmacokinetic; PWR = pediatric written request; US = United States; WW = worldwide.

3.0 SUMMARY OF PHARMACOKINETICS, PHARMACODYNAMICS AND SAFETY STUDIES IN INFANTS AGED 1 THROUGH 11 MONTHS WITH GASTROESOPHAGEAL REFLUX DISEASE

3.1 Study 3001B3-333-WW: Pharmacokinetic and Pharmacodynamic of Pantoprazole in Infants

3.1.1 Study Design

Consistent with the PWR Study 2 (PK, PD, and safety studies in infants), male and female infants ages 1 through 11 months who required pharmacological treatment with a presumptive diagnosis of GERD entered study 333. Patients received either a low dose (0.6 mg/kg equivalent) or high dose (1.2 mg/kg equivalent) of pantoprazole sodium granules for 5 to 7 days. This study characterized the PK profile of single and repeated oral doses of pantoprazole in 42 patients (21 in each dose group), and the PD profile at baseline and at steady state in 22 patients (11 in each dose group). Standard PK and PD parameters were assessed as stipulated in the PROTONIX® PWR. The major study design components, including the main inclusion criteria, were set forth by the FDA. In the battery of tests were PK and PD studies conducted in part to establish appropriate doses. Results from studies of various available PPIs in infants aged <1 year, including preterm infants and neonates, are currently being reported,[6,15,16,17,18] and some efficacy studies have also been reported.[8,19]

This was a phase 3, open-label, single- and multiple-dose PK, safety, and multiple-dose PD study in infants ages 1 through 11 months with presumed GERD. Patients received pantoprazole for approximately 5 to 10 days. Patients participated in 1 of 2 strata: PK or PD for approximately 4 weeks.

The PD response to pantoprazole after at least 5 doses (when pantoprazole is expected to reach its maximal effect [steady state]) was compared with the predose baseline findings in 2 multicenter, open-label studies. In study 1, neonates and preterm infants received pantoprazole 2.5 mg (high dose, approximately 1.2 mg/kg). Infants aged 1 through 11 months were stratified by weight and randomly assigned in a 1:1 fashion to receive pantoprazole approximately 0.6 mg/kg (low dose) or 1.2 mg/kg (high dose) (Table 3-1). Treatment was given for ≥5 consecutive days. In this study, sucralfate, bismuth preparations, misoprostil, and prokinetic agents were discontinued at least 24 h before pantoprazole administration.

Table 3-1: Pantoprazole Dose Based Upon Weight Group: Study 3001B3-333-WW

Weight (kg)	Low Dose (mg)	High Dose (mg)
2.5 to < 7	2.5	5
≥ 7 to ≤ 15	5	10

Patients were allowed to continue open-label treatment on the current dose or higher dose for an additional 6 weeks. The sample sizes for this study was based on regulatory requirements, and at least 6 patients were needed to confirm the known effect of pantoprazole on the inhibition of gastric acid in this patient population.

For PD analyses, dual-electrode 24-hour pH-metry with antimony sensors was conducted at baseline and after the final dose to analyze the effect of pantoprazole on gastric and esophageal pH. Baseline pH-metry was conducted prior to the first dose of pantoprazole (after any required PPI or H_2RA washout). After at least 5 consecutive daily doses, 24-hour pH-metry was conducted again, starting at the time of the last dose.

3.1.1.1 Patients Enrolled

Patients in this study were infants who were beyond the neonatal period (ie, they were more than 28 days of age) but less than 12 months of age, or preterm infants with a corrected age of at least 1 month but younger than 12 months corrected age at enrollment. Patients had to have a clinical diagnosis of GERD that required pharmacologic treatment in the opinion of the investigator. The method of diagnosis and any relevant tests were documented in the patient records. Body weight for PWR Study 2 (PK, PD, and safety studies in pediatric patients 1 through 11 months) had to be ≥2.5 kg to ≤15 kg. Patients in both studies must have had the ability to swallow the pantoprazole doses.

3.1.1.2 Primary and Secondary Objectives

The primary objective of study 333 was to characterize the PK profile of single and repeated oral doses of pantoprazole and the PD profile at baseline and at steady state in infants aged 1 through 11 months with presumed GERD requiring pharmacological treatment. The secondary objective was to assess the safety and tolerability of pantoprazole.

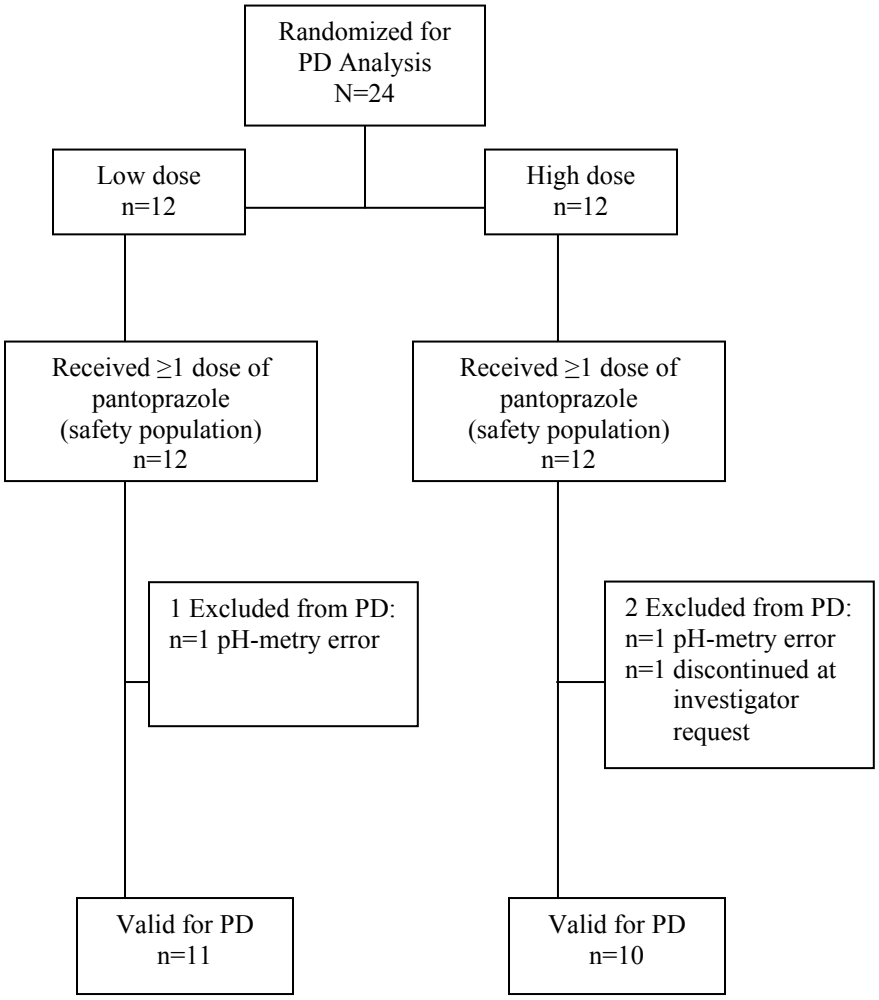
3.1.2 Summary of Results of Study 3001B3-333-WW

3.1.2.1 Population Analyzed

Sixty-seven (67) were randomly assigned to treatment and received at least 1 dose of pantoprazole. Thirty-three (33) patients were randomly assigned in a 1:1 fashion to receive the low dose (0.6 mg/kg), and 34 patients were randomly assigned to the high-dose (1.2 mg/kg) group. Forty-two (42) of the 67 patients were included in the all-patient population for single-dose PK analysis, 35 patients were included in the valid for PK evaluation population for single-dose PK analysis, and 31 patients were included in the valid for PK evaluation population for multiple-dose PK analysis.

Twenty-four (24) patients were enrolled into the PD stratum (12 randomly assigned to the low-dose group and 12 to the high-dose group (see Figure 3-1). Three (3) patients were excluded from PD analysis because of protocol violations. Twenty-one patients were evaluable for PD analyses. The safety analyses included all 24 patients.

Figure 3-1: Patient Flow Diagram for the Pharmacodynamic Analysis of Study 3001B3-333-WW



Source: Extracted from CSR-70840, study 3001B3-333-WW

The PK results from this study along with the PK profile of pantoprazole delayed-release granules in infants and children aged 1 month to 16 years has been evaluated and published.[20] The PD profile of pantoprazole delayed-release granules in infants and neonates is presented separately.[9]

3.1.3 Pharmacodynamics in Study 3001B3-333-WW

The observed results from this small study indicated that the high-dose group had higher mean values compared with the low-dose group for normalized area under the curve (AUC) of gastric H^+ activity and AUC of esophageal pH <4 at both baseline and steady state, and a higher mean value for normalized AUC of esophageal H^+ activity at baseline.

In the assessments of reflux episodes, there were no statistically significant improvements between baseline and steady state in either the number of reflux episodes, number of reflux episodes lasting more than 5 minutes, or duration of the longest reflux episode during the 24-hour pH-metry periods (Table 3-2). In the PWR Study 2, these 3 parameters were higher in the high-dose group than in the low-dose group, both at baseline and steady state.

Table 3-2: Pharmacodynamic Parameters at Baseline and After ≥5 Consecutive Doses of Pantoprazole in Infants aged 1 Through 11 Months – 24-hour Results: Study 3001B3-333-WW

Parameter	Low dose (0.6 mg/kg) (n=11)		High dose (1.2 mg/kg) (n=10)	
	Baseline	Steady State	Baseline	Steady State
Mean gastric pH	4.2 ± 1.4	4.8 ± 1.3	3.0 ± 1.4	4.2 ± 1.5[a]
Percentage of time gastric pH >4, %	55.5 ± 28.6	68.5 ± 28.3	32.2 ± 24.1	56.6 ± 31.1[a]
Normalized AUC of gastric H^+ activity, H•mmol/L	259.7 ± 442.7	102.3 ± 118.6	921.0 ± 1290.1	303.6 ± 524.9[b]
Mean esophageal pH	5.7 ± 0.7	5.6 ± 0.8	5.2 ± 0.4	4.9 ± 0.3[a]
Percentage of time esophageal pH <4 (reflux index), %	4.6 ± 3.9	4.6 ± 5.6	8.0 ± 5.6	9.4 ± 5.8
Percentage of patients with reflux index <5%, %	54.5	72.7	50.0	40.0
AUC of esophageal reflux with pH <4, pH•min	33.4 ± 25.2	24.5 ± 36.7	57.5 ± 39.3	31.3 ± 13.3
Normalized AUC of esophageal H^+ activity, H•mmol/L	2.1 ± 1.6	1.5 ± 2.4	3.5 ± 2.3	1.5 ± 0.6[a]

Abbreviation: AUC=area under the curve.
All values are mean ± SD, except for percentage of patients with reflux index <5%. P-values calculated for steady state vs baseline, and obtained from 1-sample, 2-sided, paired t-test, unless noted otherwise.
a. P<0.05
b. P=0.119; P=0.049 from Wilcoxon signed-rank test because 1 patient had an extremely large baseline value (3673 H*mmol/L).

3.1.4 Summary of Pharmacodynamics

In conclusion, the PD responses to the high dose of pantoprazole delayed-release granules showed statistically significant increases in mean gastric pH and percentage of time with gastric pH >4 but no improvement in esophageal pH. Pantoprazole in the doses administered was generally safe and well tolerated when given for up to 6 weeks. The above PD results, along with PK results of these studies,[20] suggest that the 1.2-mg/kg dose of pantoprazole for infants aged less than 1 year provides sufficient drug concentrations to significantly and reliably increase gastric pH. Many infants with a clinical diagnosis of GERD may have physiologic reflux, which does not require pharmacologic therapy. Additional research is needed to assist clinicians in diagnosing patients with pathological reflux who are unlikely to improve with age and who may require pharmacologic treatment. It is also important to clarify the relative importance of pH-metry and esophageal impedance in this process.

3.2 Supportive Study 3001B3-335-WW: Open-label Safety Extension in Infants

3.2.1 Study Design

This was an open-label, safety study in infants aged less than 12 months with presumed GERD. All patients who had successfully completed studies 3001B3-333-WW and 3001B3-331-WW at selected sites were eligible to participate. All patients who had successfully completed study 3001B3-333-WW continued on their current dose or received a higher dose based upon their clinical response or pH-metry data. Patients in study 3001B3-331-WW (preterm infants and neonates) received the 2.5-mg dose or a higher dose based upon their clinical response or pH-metry data.

All procedures from the final evaluation visit for study 3001B3-333-WW or 3001B3-331-WW were used as the on-treatment baseline for this study. Each patient participated for approximately 8 weeks including a 6-week treatment period and a 2-week follow up. Throughout the study period, routine safety of pantoprazole was monitored based on reported signs and symptoms, and the results of scheduled PEs, vital signs, length, weight, and head circumference, and clinical laboratory tests. Changes in growth parameters and their z-scores were summarized and compared within groups by a 2-sided paired t-test. The z-scores were calculated based on length-for age, weight-for-age, and head circumference-for-age charts from the US Centers for Disease Control and Prevention.

3.2.2 Objectives

The objective of this study was to assess safety and tolerability of pantoprazole in infants who had completed studies 3001B3-331-WW and 3001B3-333-WW. Growth parameters (length, weight, and head circumference) were assessed as part of the safety evaluation.

3.2.3 Patients Enrolled

Fifty-eight (58) patients enrolled in this study (9 patients from study 3001B3-331-WW and 49 patients from study 3001B3-333-WW). Twelve (12) patients were assigned to the low-dose group (0.6 mg/kg) and 46 patients were in the high-dose (1.2 mg/kg), group. All of the patients from study 3001B3-331-WW were in the high-dose (1.2 mg/kg) group. Three (3) patients were withdrawn from the study, all in the high-dose (1.2 mg/kg) group. Two (2) patients, all in the high-dose (1.2 mg/kg) group, were withdrawn from the study because of an AE, and 1 patient was withdrawn from the study because of a parental request. Fifty-five (55, 94.8%) patients completed the study.

3.2.4 Summary of Safety in Study 3001B3-335-WW

Overall, pantoprazole was safe and generally well tolerated in infants aged less than 12 months with presumed GERD who received oral doses of 0.6 mg/kg or 1.2 mg/kg daily for 6 weeks.

Statistically significant increases from both baselines (protocol 3001B3-335-WW as well as previous study baseline) to final evaluation were observed for patients within the high-dose (1.2 mg/kg) group in weight z-score for patients who participated in protocol 3001B3-331-WW (preterm infants and neonates) and in patients overall, but not for patients who participated in protocol 3001B3-333-WW. Statistically significant increases from previous studies' baseline to final evaluation was observed for patients within the high-dose group in length z-score in the patients overall, but not in the subsets of patients by previous study participation.

Statistically significant increases from previous studies' baseline to final evaluation were observed in the high-dose group in head circumference z-score for patients who participated in protocol 3001B3 331-WW and in patients overall, but not for patients who participated in protocol 3001B3-333-WW. No statistically significant difference was observed on z-score analysis between the 2 dose groups for any of the growth parameters (length, weight, and head circumference). Catch-up growth as seen in the premature infants and neonates is not unexpected for this population.

4.0 DEVELOPMENT OF SYMPTOMS ASSESSMENT TOOLS AND e-DIARY FOR PANTOPRAZOLE PEDIATRIC STUDIES

4.1 Development of the GSQ-I

The GERD Symptom Questionnaire for Infants (GSQ-I), for use by parents of infants aged 1 through 11 months, was developed to assess the response of GERD symptoms in these age groups to therapeutic treatment over a 7 –day interval.[21] Key opinion leaders, who were experts in pediatric gastroenterology, were consulted to determine which GERD symptoms would be included in the questionnaires, and the FDA was consulted for its agreement.

The GSQ-I was originally developed in a paper format and used a weekly recall period for GERD symptoms assessment.

The GERD symptoms in the questionnaires were selected to help distinguish pediatric patients who had GERD and those who did not have GERD. The questions were derived from the literature for infants[22,23,24,25,26,27] and an expert panel of pediatric gastroenterologists was consulted to assess a number of relevant GERD symptoms.

The GSQ-I was developed to assess the following symptoms: (1) vomiting or regurgitation, (2) irritability or fussiness, (3) refusal to feed, (4) choking or gagging, (5) episodes of hiccups, (6) arching back, and (7) any other symptoms related to GERD that the parent would like to record (see Section 9.1).

Frequency of symptoms was defined as the number of symptom occurrences or episodes in the 7 days before questionnaire completion; severity for each symptom was rated on a 7-point scale ranging from 1 (not at all severe) to 7 (most severe). Individual symptom scores (ISS) were calculated for each symptom and defined as the product of symptom frequency and severity. Composite symptom scores (CSS) were computed as the sum of the individual symptom scores. The ISS and CSS calculations provided information on the degree to which any specific symptom contributed to the overall symptom presentation. Face and content validity were assessed during development of the 2 GERD symptoms questionnaires through expert review of GERD symptoms, symptom definitions, and severity ratings.[21]

4.1.1 Pilot Study 3001A1-327-US

As part of the development process for GERD assessment tools in infants and young children, a pilot study (protocol 3001A1-327-US) was conducted to assess the response of GERD symptoms to therapeutic treatment in clinical trials. The publication for this study is available.[21]

This was a non-treatment, multiple-center, parallel-design, pilot study conducted at 4 centers in the United States to assess the 2 age-appropriate GERD symptoms questionnaires: the GERD symptoms questionnaire for infants (GSQ-I) (aged 1 through 11 months) and the GSQ-YC for young children (aged 1 to 5 years). Enrollment was planned for approximately 60 infants (aged 1 through 11 months) and 60 young children (aged 1 to 5 years) with and without symptomatic GERD (40 with GERD and 20 healthy controls per age cohort), but for the purpose of this briefing document, only results for infants are presented.

The objectives of this pilot study were to confirm the appropriateness and relevance of the selected GERD symptoms (ie, to test the face and content validity), to test the adequacy of frequency and severity scales (ie, to test the range of measurement that the scales permitted), to test ease of use, and to confirm that symptoms scores were higher in children with a clinical diagnosis of GERD than in healthy children.

Parents or guardians of 64 infants (1 through 11 months) completed the GSQ-I. Infants with GERD had a significantly higher prevalence of symptoms than controls, except for "refusal to feed" in infants. The most prevalent symptom among infants with GERD was vomiting/regurgitation which was significantly higher than in patients in the control group; the least prevalent symptom was refusal to feed. All symptoms occurred with significantly greater frequency in infants with GERD than in controls. Infants with GERD were reported to have more severe symptoms ($p<0.05$) than controls for all symptoms except "refusal to feed and irritability/fussiness."

The mean individual symptom score (ISS) and composite symptom scores (CSS) were significantly higher for infants with GERD than for controls, demonstrating that the 2 questionnaires were capable of differentiating infants with symptomatic GERD from healthy children and providing evidence of discriminant validity. For infants, a CSS >27 had a sensitivity of 90% for detection of patients with GERD and a specificity of 83%.

Further support was provided for the content validity of the GSQ-I based on supplemental information provided by parents and guardians indicating that the 2 questionnaires adequately captured the relevant symptoms of childhood GERD.

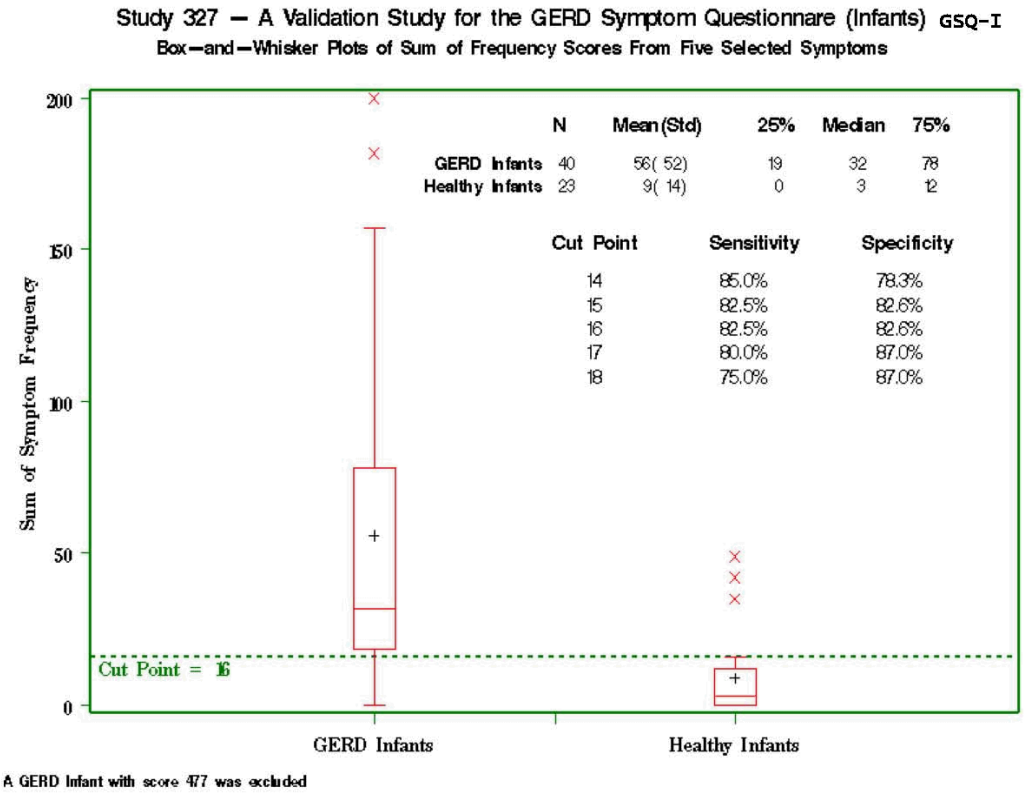
This pilot study concluded that the selected symptoms for each questionnaire were appropriate and relevant, the measurement range for frequency and severity scales was adequate for GERD evaluation, the questionnaires were easy to use, and the results showed evidence of discriminant validity because of the ability to distinguish patients with GERD from healthy control subjects.[21]

4.1.1.1 Modifications of the GSQ-I

However, modifications were recommended to be made to the GSQ-I after discussion with the FDA GI Division on 23 May 2005. The Agency suggested that the severity scores be deleted along with hiccups. Hiccups were not felt to be clinically significant symptoms. The remaining symptoms that were considered to be representative and sufficiently discriminatory for GERD in infants included the following: (1) vomiting/regurgitation, (2) irritability/fussiness, (3) refusal to feed, (4) choking/gagging when eating, and (5) arching back. As a result of the modifications to the GSQ-I, the sum of the individual frequencies were to be calculated instead of the CSS. The FDA also agreed that the modified GSQ-I could be used as screening tools for the pantoprazole efficacy studies in infants, 3001B3-329-WW.

Subsequent to these modifications, the sum of the frequency scores for the GERD symptoms for infants was re-calculated using only the 5 selected GERD symptom frequencies agreed with the FDA. The results for infants are shown graphically in Figure 4-1. GSQ-I scores calculated with the 5 selected GERD symptoms for these respective pediatric populations were then used as the basis for study entry in study 3001B3-329-WW. The cut point for confirmation of GERD diagnosis at screening would be >16 on the GSQ-I for study 329.

Figure 4-1: Sum of the Frequency Scores of 5 Selected Symptoms for Infants



A GERD infant with score of 477 was excluded.
Abbreviations: GERD = gastroesophogeal reflux disease; GSQ-I = GERD symptoms questionnaire for infants.
Source: CLINICAL R&D/CLINICAL PROTOCOLS/3001 PANTOPRAZOLE/3001B3-329-WW/.PROTOCOL AND AMENDMENTS/3001B3-329-WW Protocol - Clean Copy, Attachment 13, page 104; Amendment 3, 16 April 2007; where modified GSQ-I data from study 3001A1-327-US was presented.

Further, the FDA indicated that GERD symptoms should be collected on a daily basis because they considered a 7-day recall period too long. They recommended development of a daily GERD symptoms diary in an electronic format (e-Diary). They also suggested a small pilot test study be conducted to debug any logistic/operational issues of a daily e-Diary and to test for its ease of use. The FDA also felt that the language used in the GSQ-I was not appropriate and was not user-friendly. Wyeth suggested using wording from the I-GERQ for development of a daily e-Diary script. This was acceptable to the FDA because the I-GERQ had previously been validated for comprehension, diagnostic purposes, and outcomes. The FDA also agreed that the e-Diary script did not need to be fully validated because Wyeth did not intend to request labeling for specific GERD symptoms (see Section 9.1 for the modified GERD symptom questionnaire in infants).

4.2 Development of e-Diary

4.2.1 Pilot Study 3001B3-336-US

As suggested by the FDA, Wyeth Pharmaceuticals conducted a study to pilot test a daily e-Diary and to assess its ease of use by parents of infants from 1 month through 1 year of age and young children from 1 to 5 years of age with GERD. This was a multicenter, usual-practice study in parents of infants and young children who had been diagnosed with GERD and who were symptomatic. No study drug was administered during this study. However, for the purpose of this briefing document, only results for infants are presented.

The infant diary script (CAGS-I) consisted of 18 questions: 10 related to 5 GERD symptoms and 8 related to respiratory symptoms. Additionally, the ease of use of the e-Diary was assessed by the Feedback/Usability Questionnaire which contained 15 questions.

Forty-eight (48) parents received a hand-held e-Diary and modem to use at home to complete daily diary entries each evening assessing symptoms of his/her child's GERD symptoms over a 12 to 16 day period. Parents returned to the clinic for an end-of-study visit consisting of a final set of questions assessing issues related to ease of use and satisfaction with the e-Diary, and the clarity of e-Diary items and instructions. Summaries of answers to the feedback/usability questionnaire were assessed to determine the usability of e-Diaries (primary goal for this study). Summaries of GERD and respiratory symptom scores were also reported.

The e-Diary for infants included a symptoms script that prompted parents to assess the frequency of GERD symptoms during the previous 24-hour period. The script, called the Caregiver Assessment of GERD Symptoms in Infants (CAGS-I), was based on the modified GSQ-I, which

was previously developed to assess GERD symptoms in infants aged 1 through 11 months (see Section 9.1 for the modified GERD symptom questionnaire in infants and Section 9.2 for e-Diary script).

The parents of the 24 infants completed the study. The mean age of the infants was 24.25 weeks (SD ±11.47 weeks; range 4 to 45 weeks). The mean age of the young children in the study was 2.91 years (SD ±1.49 years; range 1 to 5.92 years). Most of the pediatric participants were male (63% and 71% of the infants and young children, respectively).

Parents of infants were compliant with completing the diaries. Compliance was 97% for each of the 5 individual GERD symptoms questions for parents of infants. These results were similar to those reported in the literature by Laurisen of 92%.[28] Parents of infants preferred to complete the diary in the evening. They found the e-Diary instructions to be clear, response options to be sensible, and the diaries not to be too complex. In general, the e-Diaries were felt to be easy to use, and were liked by parents. For validity, the internal consistency reliability among the questions pertaining to the overall ease of using the e-Diary on the feedback/usability questionnaire was high (Cronbach's coefficient alpha 0.76), which was considered acceptable.

The correlation coefficients between week 1 and week 2 for the WGSS of the 5 individual GERD symptoms scores ranged from 0.79 to 0.95 based on data collected using the e-Diaries for infants. All correlation coefficients were significantly different from zero ($p<0.0001$).

The most commonly reported symptoms in infants were: vomiting/regurgitation, irritability/fussiness, and arching back. The relative symptom frequencies were very similar to those previously reported using the GSQ-I questionnaires that used a weekly recall,[21] as well as with the medical literature.[22,29]

Parents of infants reported an average of a once-a-week occurrence of a cold or fever. Respiratory symptoms (cough or noisy breathing) in the absence of a cold or fever were reported commonly in infants, mean average of weeks 1 and 2 = 0.8 and 0.7, respectively but did not occur much of the time during the day. Parents identified wheezing more commonly than stridor. The results showed that parents may have had difficulty distinguishing wheezing from stridor.

Overall, the daily diary scripts used in the e-Diaries presented GERD and respiratory symptom questions in an easy-to-understand and complete format that was very acceptable to parents of

infants with GERD. Compliance with the e-Diaries was high (97% for parents of infants) and the data received were very consistent on a day-to-day and week-to-week basis. The data were also consistent with previous reports.[22,29]

Findings in this study were used by Wyeth Pharmaceuticals to further refine the development and implementation of the age-appropriate e-Diaries to assess GERD in infants.

5.0 STUDY 3001B3-329-WW: EFFICACY AND SAFETY EVALUATIONS IN INFANTS

5.1 Study Design

The design of study 3001B3-329-WW (329) was consistent with the pantoprazole PWR Study 3 (Efficacy and Safety Evaluation of Pediatric Patients 1 to 11 Months of Age) in infants and was a phase 3, multicenter, outpatient, randomized, double-blind, placebo-controlled, treatment-withdrawal study in infants, 1 through 11 months of age, with symptomatic GERD. This study was designed to demonstrate the efficacy and safety of pantoprazole in infants beyond the neonatal period but less than 1 year of age with symptomatic GERD. Study entry required that the GERD symptoms on the GERD Symptom Questionnaire for Infants (GSQ-I) was > 16. To be eligible for inclusion in this study, patients had to have a GSQ-I total symptom frequency score > 16 at screening and baseline. The GSQ-I assessed the frequency of the 5 GERD symptoms in infants over the preceding 7 days: 1) vomiting/regurgitation, 2) choking/gagging, 3) arching back, 4) irritability/fussiness, and 5) refusal to feed. The diagnostic cut point of > 16 for the GSQ-I was based upon data from the initial validation study 327.[21] The cut-off of > 16 was previously demonstrated to distinguish infants with GERD from normal infants. The study consisted of a 2-week screening period during which all patients received conservative therapy. Conservative therapy included feeding modifications (use of a protein-hydrolysate formula thickened with one tablespoon of dry rice cereal per ounce as smaller, more frequent feedings), positioning (changes included avoidance of seated and supine positions).[30] Patients remaining symptomatic at the end of the 2-week screening period entered a 4-week open-label phase in which they received pantoprazole treatment and subsequently were randomized to receive pantoprazole treatment or placebo for an additional 4 weeks.

This study consisted of 3 periods:

1) Screening period (approximately 2 to 4 weeks)

a. All patients received standard conservative treatment for GERD including hypoallergenic formula thickened with rice cereal, standardized advice for parents. Conservative therapy was continued throughout the study.
b. Specified study calcium-containing rescue antacid (MYLANTA® Supreme or local country equivalent) not to exceed 35 mg Ca^{++}/kg/day or 87.5 mg $CaHCO_3$/kg/day was allowed as needed after ≥5 minutes of severe GERD symptoms, as determined by the caregiver. Hypoallergenic formula, rice cereal as well as rescue antacids were provided by the sponsor.
c. Patients who improved on the 2-week conservative treatment and had GSQ-I scores ≤ 16 were excluded from the study.

2) Treatment period (8 weeks) that consisted of 2 parts in which patients were stratified by weight prior to each 4 week phase:
   a. A 4-week open-label (OL) treatment run-in phase followed by
   b. A 4-week double-blind, placebo-controlled withdrawal phase,
3) Follow-up period (2-weeks).

Two (2) strengths (5.0 and 10.0 mg) of pantoprazole were dispensed by weight group according to Table 5-1 to achieve an approximate daily dose of 1.2 mg/kg. The dose, 1.2 mg/kg of pantoprazole sodium granules was chosen on the basis of preliminary PK data from protocol 3001B3-333-WW, which was conducted in a similar patient population (infants aged 1 through 11 months with GERD).

Table 5-1: Pantoprazole Dose Administration According to Weight Group - Study 3001B3-329-WW

Weight (kg)	Approximate Dose Strength: 1.2 mg/kg
≥2.5 kg to <7 kg	5.0 mg
≥7 kg to ≤15 kg	10.0 mg

Patients who were ≥80% compliant during the OL phase and whose symptoms had improved in the opinion of the investigator entered the DB treatment-withdrawal phase, at which time they were randomly assigned in a 1:1 fashion stratified by weight to receive pantoprazole or placebo for an additional 4 weeks.

5.1.1 GERD Diagnosis

Diagnostic testing is often required to confirm the diagnosis of GERD in infants. Esophageal pH monitoring is used to measure the presence of abnormal acid reflux. Esophagastroduodenoscopy

(EGD) is used to determine the presence and severity of esophagitis, strictures, and Barrett's esophagus, as well as to exclude other disorders (eg, Crohn's disease and eosinophilic or infectious esophagitis).[31,32,33,34,35] Upper gastrointestinal (GI) series and scintigraphy (radionuclide milk study) may also be used in the evaluation of GERD in infants.[4]

In study 329, the method by which the clinical diagnosis of suspected, symptomatic, or endoscopically proven GERD was made were recorded and summarized for each patient. These summaries included the clinical history, GSQ-I (baseline total symptom frequency), and the results of laboratory tests used to establish the diagnosis (eg, pH probe, gastroesophageal endoscopy, esophageal history, *H. pylori* rapid urease or breath test, laryngoscopy, radionuclide milk study, and upper GI series). Documentation of all diagnostic tests, which were performed during routine patient care to document the diagnosis of GERD whether or not they support the diagnosis were maintained.

5.1.2 Patients Enrolled

Patients were post-term infants older than 28 days but younger than 12 months of age, or preterm infants with a corrected age of 44 weeks or older but younger than 12 months at the time of informed consent; weight was required to be 2.5 kg to ≤15 kg. Patients were required to have a modified total GERD Symptom Questionnaire in Infants (GSQ-I)[21] mean symptom frequency >16 at screening and baseline and a clinical diagnosis of suspected, symptomatic, or endoscopically proven GERD (erosive or histologic esophagitis). Exclusion criteria included a known history or presence of upper gastrointestinal (GI) anatomic or motility disorders or clinically significant medical conditions as indicated by physical examination, electrocardiogram (ECG), or laboratory test; use of PPIs or H_2RAs within 14 days of completion of the GSQ-I baseline questionnaire; or use of any nonstudy medication for treatment of a GI condition within 3 days before completion of the GSQ-I baseline questionnaire. In addition, patients could not have any disorder requiring daily use of warfarin or other anticoagulants, carbamazepine, phenytoin, or anticholinergics.

Medications to treat non-GI conditions were allowed as needed at stable doses with the exception of glucocorticoids (except topical or inhaled), prostaglandins, or anticoagulants. Any medication used to treat a GI condition or any supplement or herbal medication that could interfere with the metabolism of pantoprazole was not allowed.

5.1.3 Primary and Secondary Efficacy Variables

The primary efficacy endpoint was the actual withdrawal due to lack of efficacy during the double-blind, placebo-controlled withdrawal phase. Lack of efficacy was defined as 1 or more of the following conditions:

- Significant worsening of GERD symptom frequency (ie, WGSS returned to baseline or above on 2 consecutive weekly evaluations not related to an intercurrent illness).
- A diagnostic test such as endoscopy demonstrating the worsening of esophagitis.
- Maximal antacid use for ≥7 continuous days.
- Severe GERD symptoms based on physician's judgment, not related to intercurrent illness, as documented at an unscheduled or scheduled visit.

The WGSS is derived as the sum of the 5 selected individual weekly GERD symptoms mean frequencies during the previous 24-hour period: 1) vomiting/regurgitation, 2) choking/gagging, 3) arching back, 4) irritability/fussiness, and 5) refusal to feed. These were collected daily via an electronic diary (e-Diary). The GSQ-I was modified for use as a daily e-Diary using questions from the I-GERQ validated infants symptom tool developed by Orenstein et al.[22,29]

The secondary endpoints were as follows:

- Lack of efficacy per withdrawal criteria.
- Withdrawal for any reason.
- Time to withdrawal due to lack of efficacy, time to meeting the criteria for lack of efficacy, and time to withdrawal for any reason.
- WGSS and individual mean frequency for each GERD symptom.
- The amount of antacid taken during each week and biweekly (ie, every 2 weeks).
- The number of patients taking antacids during each week and biweekly.
- Respiratory symptoms, eg, frequency of cough, noisy breathing in or out, breathing with a wheezy sound, breathing with a croupy sound, and stopped breathing (apnea).

During the study, e-Diaries were distributed to the parents of patients (or the primary caregiver living with the patient) of patients who satisfied the inclusion/exclusion criteria at the end of the screening visit (day -14). They were to be completed daily each evening and the e-Diary questions assessed GERD symptoms using 24-hour recall during screening and for 8 weeks during treatment. The GSQ-I was modified for use as a daily e-Diary using questions from the I-GERQ validated infants symptom tool developed by Orenstein et al.[29]

An e-Diary was used to primarily assess the daily frequency of the following 5 selected individual weekly GERD symptom mean frequencies for 1) vomiting/regurgitation (Q1a); 2) irritability/fussiness (Q2b); 3) choking/gagging (Q3a); 4) arching back (Q4a); and 5) refusal to feed (Q5a/5b). The frequencies of respiratory symptoms were also collected using the e-Diary (cough without a cold, aspiration/cough after choking/gagging, wheezing, apnea, and stridor). In addition, antacid usage and administration of study drug were reported using specific questionnaires in the e-Diary (Section 9.2). Details of e-Diary implementation for study 329 are provided in Section 5.1.4.

A weekly GERD symptom score (WGSS) was calculated for the week before the patient received the open-label test article and for each week of treatment during the open-label and double-blind phases. The WGSS was derived as the sum of the 5 selected individual GERD symptom weekly mean frequencies. WGSS was a secondary endpoint in the study and was used as one of the withdrawal criteria.

5.1.4 Implementation of the Infant e-Diary in Study 3001B3-329-WW in Infants Aged 1 Through 11 Months

An e-Diary was distributed to the parents (or the primary caregiver living with the patient) of patients who satisfied the inclusion/exclusion criterion at the end of the screening visit (day -14). They were to be completed daily, in the evening between 6 to 12 pm. The e-Diary script assessed GERD symptoms using a 24-hour recall. Daycare and preschool providers must have been willing to provide GERD and respiratory symptom information to the parent. Daycare providers were given information to alert them regarding the GERD and respiratory symptoms that were collected in the e-Diary. This information may have been provided verbally to the parent.

The e-Diary script was used primarily to assess the frequency of the following 5 GERD symptoms during the previous 24-hour period during screening and for 8 weeks during treatment: (1) vomiting/regurgitation, (2) choking/gagging, (3) arching back, (4) irritability/fussiness, and (5) refusal to eat. The frequency of respiratory symptoms were also collected using the e-Diary (cough without a cold, aspiration/cough after choking/gagging, wheezing, apnea, and stridor). In addition, antacid usage and administration of test article were recorded using specific questions in the e-Diary.

Total GERD mean symptom frequency was calculated for the week (WGSS) before the patient received the open-label test article, and for each week of treatment during the open-label and double blind phases. The WGSS was derived as the sum of the 5 selected individual GERD symptoms weekly mean frequencies and was based on data collected daily in the infant e-Diary using the infant diary script (CAGS-I). A Weekly GERD Symptom Score (WGSS) was defined as the sum of the 5 selected individual weekly GERD symptom mean frequencies for vomiting/regurgitation (1a), irritability/fussiness (2b), choking/gagging (3a), arching back (4a) and refusal to feed (higher score of 5a and 5b). WGSS was a secondary endpoint in the study and was used as one of the withdrawal criteria.

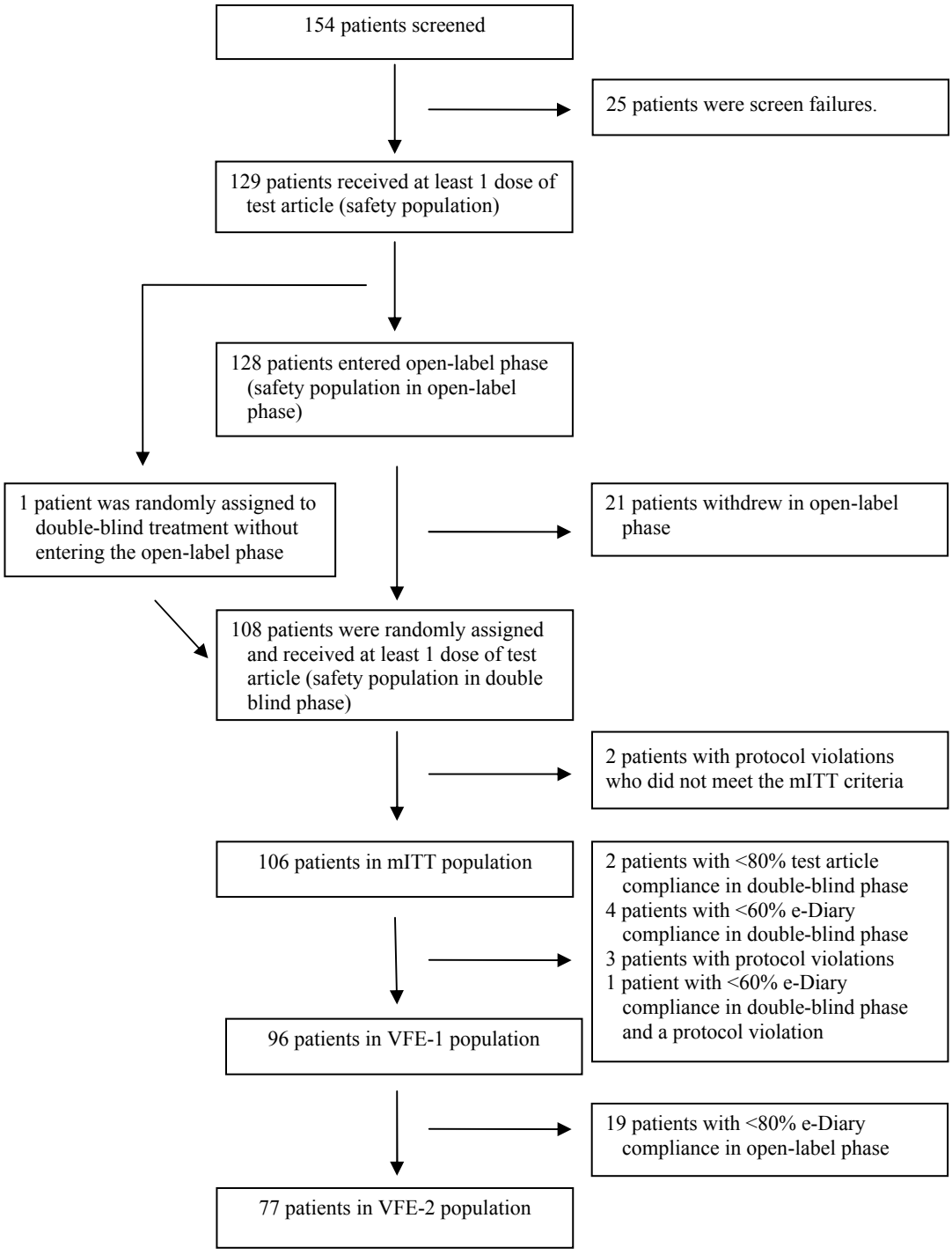
5.2 Results of Study 3001B3-329-WW – Infants 1 Through 11 Months

5.2.1 Population Analyzed

A total of 154 patients with GERD symptoms were screened at 31 investigative sites. Of the 25 screen failures, 6 did not meet inclusion criteria, 3 had clinically significant abnormal laboratory test results, and the rest were due to poor compliance/noncompliance, parental request, or withdrawal of consent. Of the 6 who did not meet inclusion criteria, 5 had improved GSQ-I scores following the 2 weeks of conservative treatment and no longer met the criterion of a GSQ-I score >16, which was far less than the 24% improvement rate with conservative treatment that was reported by Shalaby and Orenstein from a primary care setting.[30] One patient did not meet the age requirements.

A total of 129 patients received at least 1 dose of pantoprazole (safety population). Twenty-one (16.4%) patients were withdrawn from the study during the OL phase, the most common reason being parental noncompliance with electronic diary completion in 9 patients (7.0%) and adverse events and parental request in an additional 4 (3.1%) patients each. A total of 106 patients received DB treatment and comprised the mITT population (Figure 5-1).

Figure 5-1: Patient Disposition: Study 3001B3-329-WW



Abbreviations: mITT = modified intent to treat; VFE = valid-for-efficacy.

Twenty (18.5%; pantoprazole n=11, placebo n=9) patients were discontinued during the DB phase. Lack of efficacy accounted for most study discontinuations; details are presented in the efficacy Section 5.2.3, below. Of discontinuations for reasons other than lack of efficacy, 4 (3.7%) were due to protocol violation, 2 (1.9%) were due to noncompliance with the study protocol, and parental request or failure to return accounted for 1 patient each (0.9%).

In the mITT population, the majority of patients were white males whose mean age was 5.1 months (see Table 5-2). The mean corrected age of pantoprazole preterm infants (5.42 months, n=9) was greater than that of placebo preterm infants (3.15 months, n=10); however, the overall calculated mean population ages and all other demographic data were comparable between treatment groups. Approximately one-third of the patients had had any previous diagnostic tests for GERD at baseline (15 [28.8%] and 20 [37.0%], pantoprazole and placebo, respectively); a diagnosis of GERD was suggested or confirmed in 10 (19.2%) and 13 (24.1%) of these patients, respectively. Mean baseline GSQ-I scores were also similar between treatment groups. The baseline GSQ-I score was highly correlated with the baseline WGSS ($r=0.747$, $p<0.0001$). Of the safety population, approximately 56 (43.4%) had used medication for GERD before study entry.

Table 5-2: Baseline Demographics and Clinical Characteristics, Modified Intent-to-Treat Population: Study 3001B3-329-WW

	Pantoprazole (n = 52)	**Placebo (n = 54)**
Full term[a] - n (%)	43 (82.69)	44 (81.48)
Age, months - mean (SD)	5.15 (2.81)	5.04(2.81)
Age or corrected age,[b] months - mean (SD)	4.91 (2.72)	4.79 (2.87)
Male- n (%)	34 (65.38)	34 (62.96)
Race - n (%)		
White	35 (67.31)	35 (64.81)
African American	10 (19.23)	10 (18.52)
Asian	6 (11.54)	5 (9.26)
Other	1 (1.92)	3 (5.56)
Weight, kg - mean (SD)	7.08 (1.90)	6.90 (1.66)
Height, cm – mean (SD)	64.0 (6.51)	64.1 (5.82)
GSQ-I symptom frequency – mean	114.8 (73.80)	106.5(72.49)
Diagnosis of GERD – n (%)		
Tests performed	15 (28.8)	20 (37.0)
Test results reported as consistent with GERD	10 (19.2)	13 (24.1)

GERD = Gastroesophageal reflux disease; GSQ-I = GERD Symptom Questionnaire (ref)
a. Gestation ≥ 37 weeks
b. Pre-term infants

5.2.2 Compliance

Mean compliance with study medication in the DB phase was 97.7% and 97.6%, pantoprazole and placebo, respectively. Mean compliance with electronic diary completion in the mITT population during the OL phase was 87.83% with a minimum of 60.71%. In the DB phase, overall mean compliance was 84.54% with a minimum of 32.14%. There were no significant between-group differences during either treatment phase.

5.2.3 Efficacy Results in Infants 1 Through 11 Months

In the DB phase, 6 patients in each treatment group were withdrawn from the study due to lack of efficacy. There were no significant between-group differences in rates of withdrawal due to lack of efficacy, lack of efficacy per withdrawal criteria or withdrawal for any reason (see Table 5-3).

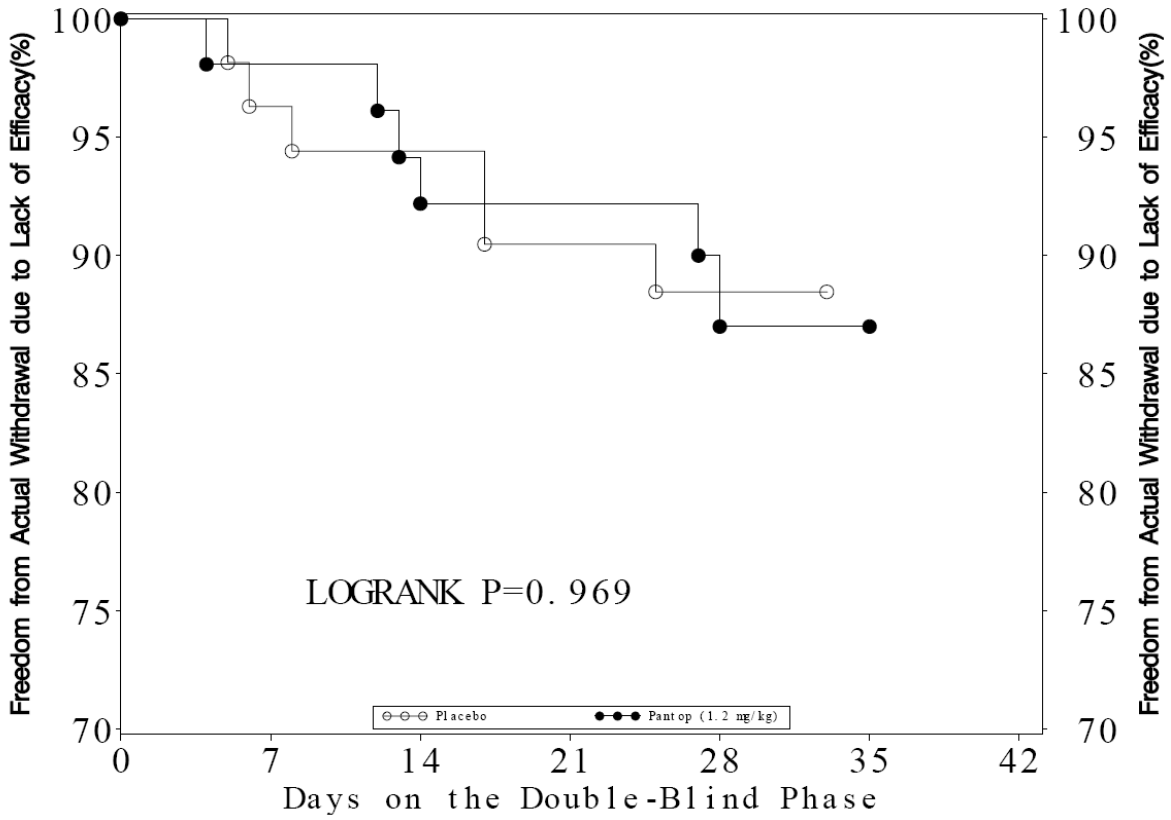
Table 5-3: Withdrawal During the Double-Blind Phase, Modified Intent-to-Treat Population: Study 3001B3-329-WW

Reason for withdrawal, n (%)	Pantoprazole n=52	Placebo n=54
Actual withdrawal due to lack of efficacy	6 (11.5)	6 (11.2)
Lack of efficacy per withdrawal criteria*	8 (15.4)	8 (14.8)
Withdrawal for any reason	9 (17.3)	9 (16.7)

*Patients who met criteria for withdrawal but may or may not have been withdrawn at the discretion of the investigator

Kaplan-Meier estimates and log-rank tests were used to compare the time to actual withdrawal from the study due to lack of efficacy between treatment groups. The estimated time to withdrawal from the study is presented for the mITT population in Figure 5-2.

Figure 5-2: Kaplan-Meier Plot of Time to Actual Withdrawal Due to Lack of Efficacy During the Double-Blind Phase – mITT Population in Study 3001B3-329-WW

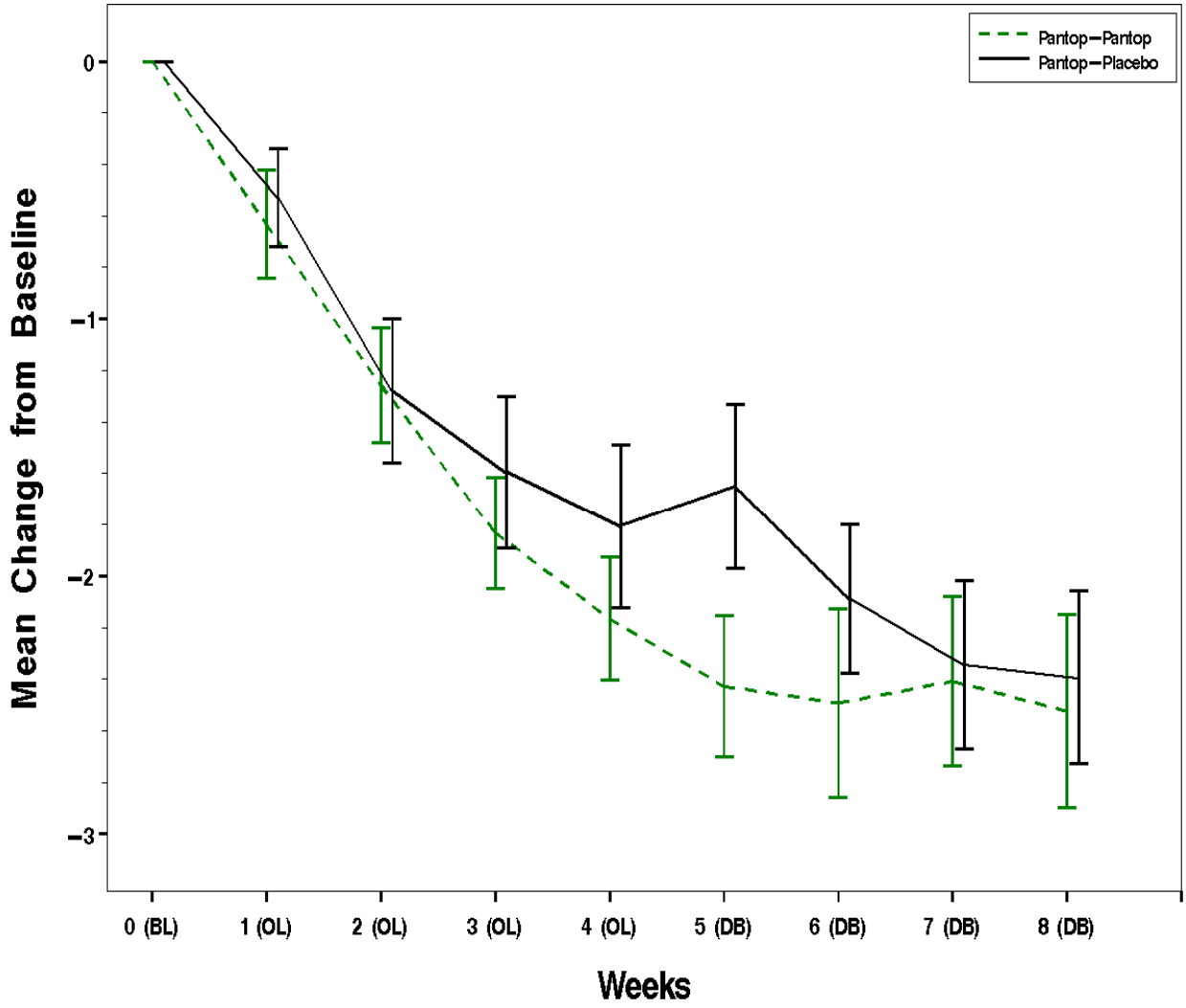


Abbreviation: mITT=modified intent-to-treat.
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/3001B3 PANTOPRAZOLE/P329/kmplots.ppt.

There was no significant difference between the pantoprazole-treated patients and the placebo-treated patients in the time to withdrawal due to a lack of efficacy of the test article.

Significant cumulative reductions from baseline in weekly GERD symptom score (WGSS) were observed each week during the 4 weeks of the open-label treatment run-in phase where all patients received pantoprazole 1.2 mg/kg (p-value < 0.001). This improvement was maintained during the double-blind phase. After randomization there was no significant difference between groups as presented in Figure 5-3 and Table 5-4. The direction of the changes in the WGSS showed continued improvement during the double-blind phase from the open-label phase in the pantoprazole 1.2 mg/kg group (see Figure 5-3).

Figure 5-3: Mean Change (± SE) in WGSS During Open-Label and Double-Blind Treatment Phases by Treatment Group: Last Observation Carried Forward - Infants 1 Through 11 Months: Study 3001B3-329-WW



Abbreviations: WGSS=Weekly GERD Symptom Score; SE = standard error; BL=baseline; OL = open-label; DB = double-blind.
Note: The study design encompassed two 4-week treatment phases: an initial open-label phase with pantoprazole treatment and a double-blind treatment-withdrawal phase.
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/3001B3 PANTOPRAZOLE/P329 /3001-P329 gerdbywk.rtf

Table 5-4: Summary of the Weekly GERD Symptom Score From Baseline to the Final Evaluation - Infants 1 Through 11 Months in mITT Population: Study 3001B3-329-WW

		------ Treatment Group[a] ------	
Study Week	Weekly GERD Score[b] Statistics	Pantoprazole/ Placebo (n=54)[c]	Pantoprazole/ Pantoprazole (n=52)[c]
Week -1 (Baseline)	Mean ± Standard deviation	5.25 ± 2.93	5.72 ± 2.73
Week 4 (OL)	Mean ± Standard deviation	3.44 ± 2.37	3.55 ± 2.44
Change from Baseline			
	Mean ± Standard deviation	-1.81 ± 2.33	-2.17 ± 1.72
	p-value[e]	< 0.001	< 0.001
Final Week[d]	Mean ± Standard deviation	2.88 ± 1.98	3.31 ± 2.57
Change from Baseline			
	Mean ± Standard deviation	-2.38 ± 2.46	-2.41 ± 2.70
	p-value[e]	< 0.001	< 0.001

Abbreviations: GERD = Gastroesophageal Reflux Disease; OL=open-label; DB=double-blind; mITT = modified intent-to-treat.

Note: The study encompassed two 4-week treatment phases: an initial 4-week of open-label phase and a 4-week of double-blind treatment-withdrawal phase.

a. Data are summarized by treatment group as randomized at the end of week 4. All patients received 1.2 mg/kg pantoprazole during the open-label phase (from week 1 through week 4).
b. Weekly GERD symptom score is defined as the sum of the 5 weekly mean frequency scores for e-Diary items.
c. Last observation carried forward.
d. Final week is the last 7 days of symptom scores collected during the double-blind phase.
e. p-Value is obtained from the 2-sided paired t-test.

Source: Extracted from: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/3001B3 PANTOPRAZOLE/P329/3001-P329 tab02_2 – 11APR08 12:17.

Individual symptom scores decreased in both groups in both OL and DB phases, with arching back and crying/irritability accounting for 55% of the overall change (Table 5-5).

Table 5-5: Mean Change from Baseline, Weekly GERD Symptom Scores by Individual Component Score, Modified Intent-to-Treat Population: Study 3001B3-329-WW

	Pantoprazole-Pantoprazole n=54				Pantoprazole-Placebo n=52			
	Mean (SD) Change from Baseline, Week 4	p-value	Mean (SD) Change from Baseline, Week 8	p-value	Mean(SD) Change from Baseline, Week 4	p-value	Mean(SD) Change from Baseline, Week 8	p-value
Total WGSS	-1.81 (2.33)	<0.001	-2.39 (2.47)	<0.001	-2.17(1.72)	<0.001	-2.52 (2.70)	<0.001
1a:Vomiting/regurgitation Frequency	-0.45 (0.68)	<0.001	-0.62 (0.72)	<0.001	-0.41 (0.52)	<0.001	-0.48 (0.87)	<0.001
2b: Irritability/fussiness	-0.39 (0.58)	<0.001	-0.49 (0.57)	<0.001	-0.55 (0.55)	<0.001	-0.64 (0.72)	<0.001
3a: choking/gagging	-0.36 (0.51)	<0.001	-0.40 (0.60)	<0.001	-0.38 (0.49)	<0.001	-0.42 (0.66)	<0.001
4a: Arching back	-0.34 (0.64)	<0.001	-0.50 (0.79)	<0.001	-0.58 (0.77)	<0.001	-0.73 (0.99)	<0.001
5a/b: Refusal to feed	-0.27 (0.59)	0.002	-0.38 (0.63)	<0.001	-0.25 (0.49)	0.001	-0.26 (0.63)	0.005

Abbreviations: GERD = Gastroesophageal Reflux Disease; SD = standard deviation; WGSS=Weekly gastroesophageal reflux disease symptom score

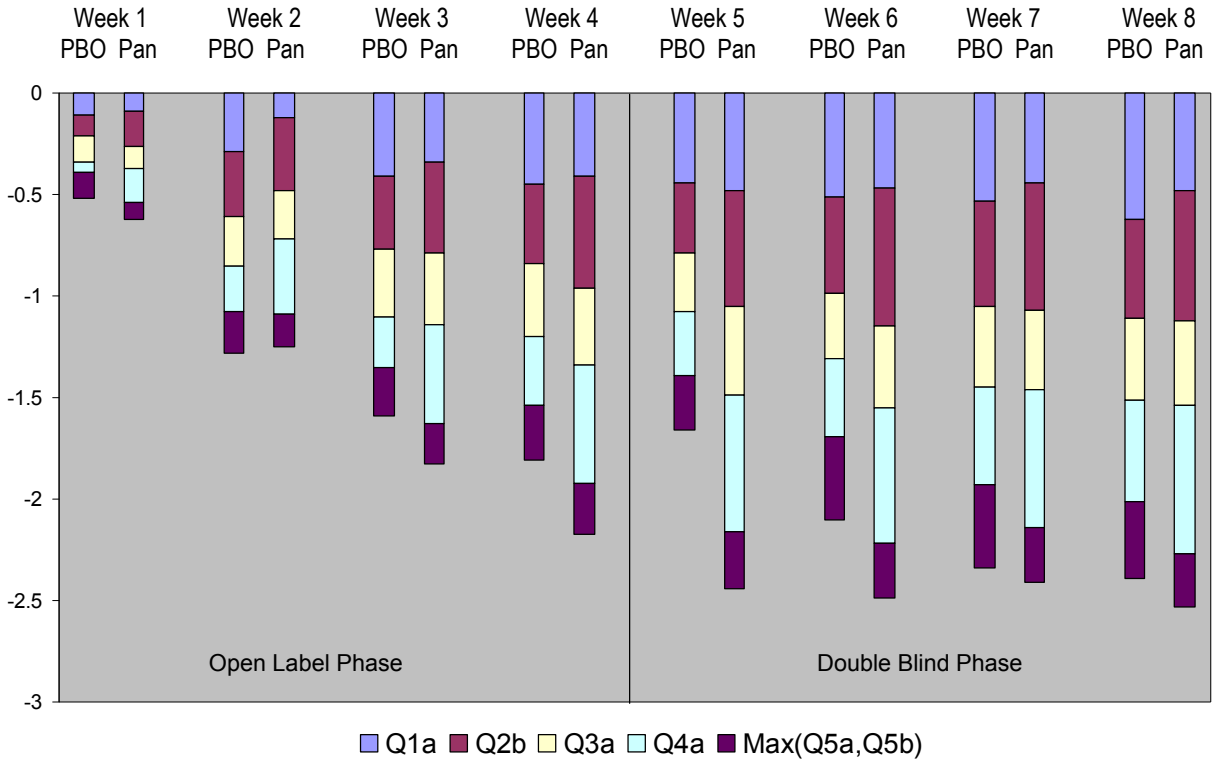
The observed between-group difference in the overall WGSS change at week 5 was primarily due to a greater decrease in episodes of arching back with pantoprazole than placebo (p=0.028). With the exception of vomiting/regurgitation, the percentage of patients reporting each individual symptom decreased by >10% from baseline to week 4 and decreased further by approximately 10% for each symptom to week 8. The reductions in the percentage of patients reporting each symptom were similar between the 2 treatment groups.

Figure 5-4 depicts graphically the relative contribution of each symptom to the observed decrease in the WGSS. The components appear in separate bar segments for Q1a, Q2b, Q3a, Q4a, and Q5a/5b. Changes to WGSS are shown for weeks 1 through 8, with separate bars for the pantoprazole 1.2 mg/kg ("Pan") group and the placebo ("PBO") group. All GERD symptoms decreased from baseline. The greatest change was seen in a reduction in arching back (Q4a) and crying/irritability (Q2b), which represented approximately 55% of the change. The smallest improvement occurred in the refusal to feed (Q5a/5b).

At week 5, continued improvements were seen in each of the individual symptom scores in the pantoprazole 1.2-mg/kg group (the WGSS mean change from week 4 was -0.26 (p=0.155). In contrast, the corresponding values for the placebo group showed slight increases in each individual symptom score (the WGSS mean change from week 4 was 0.15; p=0.384).

The direction of the changes in the WGSS and individual symptom scores showed continued improvements during the double-blind phase from the open-label phase in the pantoprazole 1.2-mg/kg group. There appeared to be a slight withdrawal effect in the placebo group during the week 5 of the double-blind period. However, no relapse of symptoms were essentially seen in the placebo group from week 6 throughout the remainder of the double-blind phase.

Figure 5-4: Changes From Baseline in Weekly GERD Symptom Scores by Individual Component Score: Study 3001B3-329-WW



Abbreviations: GERD=gastroesophageal reflux disease; PBO=placebo; Pan=pantoprazole 1.2 mg/kg; Q1a=vomiting/regurgitation (item 1a); Q2b= fussiness (item 2b); Q3a=choking/gagging (item 3a); Q4a=arching back (item 4a); Max(Q5a,Q5b)=refusal to feed (maximum of items 5a and 5b).
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/3001B3 PANTOPRAZOLE/P329/ stacked bar graph2.xls.

In addition, the weekly mean score for the amount of spitting up (Q1b) and duration of fussiness (Q2c) decreased significantly each week during the open-label phase ($p<0.001$). During the double-blind phase, the improvements in weekly mean score achieved during open-label treatment with pantoprazole were maintained with both the pantoprazole and the placebo group treatments. Between-group comparisons showed no significant differences at each week in the double-blind phase.

The mean amount of antacid taken weekly decreased significantly from baseline (11.9 mL) to week 4 in the overall population (6.7 mL; $p<0.001$, change from baseline), as well as from baseline to week 8 in both treatment groups (5.1 mL and 4.1 mL, pantoprazole and placebo, respectively; $p<0.005$). The percentage of patients taking antacids at least once weekly also decreased from baseline (62.5%) to week 4 (47.9%) and to week 8 in each group (39.1% and

32.6%, pantoprazole and placebo, respectively). There was no significant between-group difference in any measure of antacid use during the DB phase.

5.2.3.1 Respiratory Symptoms Discussion

Parents had difficulty distinguishing symptoms related to breathing in or out. Noisy breathing out should have been similar to wheezing, and noisy breathing in should have been similar to breathing with a croupy or barky sound, but the results were quite different. Parents were able to report noisy breathing and cough without a cold more reliably.

The groups were unbalanced at baseline, with more patients having noisy breathing and cough without a cold in the pantoprazole 1.2-mg/kg group. In general, weekly mean scores for individual respiratory symptoms decreased statistically significantly with greatest reduction observed during the 4-week open-label run-in phase ($p=0.004$ to $p<0.001$). Between-group differences were not statistically significant during the double-blind phase. Cold or fever occurred approximately 25% of the time in both treatment groups. Breathing with a croupy or barky sound was infrequently (9%) reported at baseline. Apnea was rarely reported and occurred only 1% to 2% of the time throughout the study. These symptom scores do not change significantly with treatment.

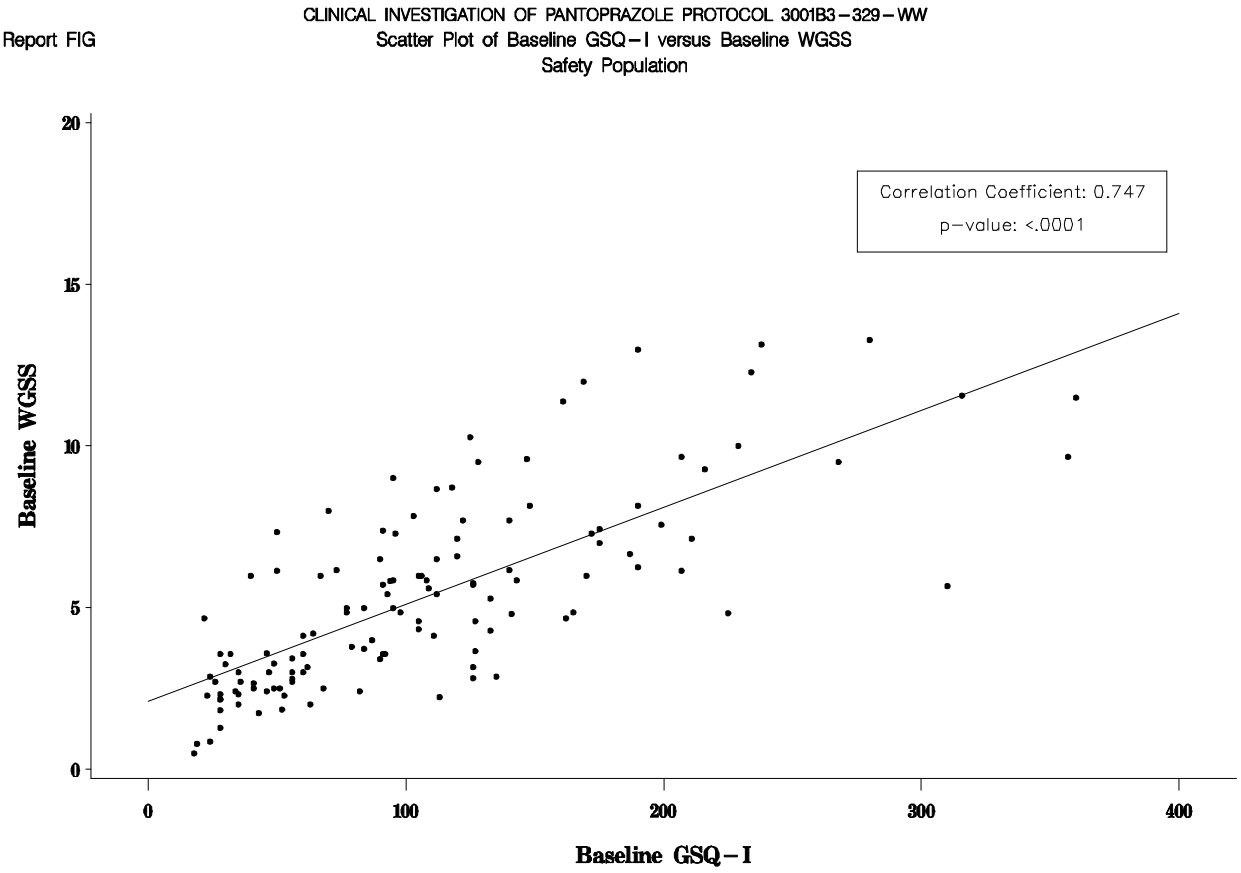
Improvements in these symptoms were seen with the greatest improvement during the first 4 weeks of treatment. It is difficult to attribute any causal relationship between treatment and improvement in respiratory symptoms, but an improvement was observed. Apnea was rarely reported, and no effect on apnea was observed with treatment.

5.2.4 Compliance with the e-Diary and Correlation with GSQ-I

During this study, parents of infants were compliant in completing the e-Diary, with no differences observed among the pantoprazole treatment group and the placebo group. Mean compliance during the study was approximately 88% (±9.1, range 65% to 100%).

The correlation of the WGSS at baseline and the GSQ-I symptom frequency score at baseline are shown in Figure 5-5. The WGSS and GSQ-I scores were significantly correlated at baseline (correlation coefficient 0.747, $p<0.0001$). This suggests that the WGSS, derived from data collected in the infant e-Diary, produced GERD symptoms assessments comparable with the GSQ-I tool which had been validated in a previous pilot study.

Figure 5-5: Correlation of Baseline GSQ-I and Baseline WGSS (Study 3001B3-329-WW)



Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3001B3 /329/Final/fig_wgss.rtf (Jun 26, 2008 8:40:01 AM).

Study 329 demonstrated the ability of the e-Diary to collect GERD symptoms from parents of infants aged 1 through 11 months during pantoprazole treatment, with an overall compliance of 88%. Baseline GSQ-I and WGSS results were significantly correlated. During the study, GERD symptoms decreased significantly over the first 4 weeks with pantoprazole treatment and sustained the scores till the end of the study.

5.3 Summary and Conclusions - Study 3001B3-329-WW

The primary assessment of efficacy was the actual withdrawal due to lack of efficacy during the double-blind, placebo-controlled withdrawal phase. No treatment effect was observed on withdrawal rates for lack of efficacy, on the percent of patients meeting the criteria for lack of efficacy, or on withdrawal rates for any reason. GERD symptoms improved with treatment in the open-label phase of the study and generally continued to improve during the double-blind phase, suggesting a durable effect. There were no significant differences between patients

receiving continued pantoprazole treatment and patients receiving placebo; hence, no effects of treatment withdrawal were observed in the double-blind phase.

Pantoprazole sodium 1.2 mg/kg was effective in reducing symptoms of GERD in infants with a clinical diagnosis of GERD. After 4 weeks of treatment, the majority of patients treated with placebo along with conservative treatment and rescue antacids continued to do well and were indistinguishable from those who continued treatment with pantoprazole 1.2 mg/kg.

Pantoprazole was safe and well-tolerated. None of the SAEs and few TEAEs were considered to be related to study drug. Changes in laboratory test results, ECG findings, and vital sign measurements were also considered to be minor, with few considered to be AEs by the investigators. All infants grew normally during the study with no significant differences between groups.

The results of this study suggest that extensive conservative treatment along with rescue antacids plus possibly a 4 to 5 week course of PPIs may be sufficient for the majority of infants with symptomatic GERD. Patients with more severe symptoms or failure of conservative treatment might benefit from objective testing to assess their disease and to exclude other disorders such as cow's milk allergy, eosinophilic esophagitis, and infantile colic, which are often confused with GERD. Only infants with clinically significant GERD should be considered for longer term pharmacologic therapy.

For additional discussion see Section 7.0.

6.0 CHALLENGES IN PERFORMING STUDIES IN INFANTS

There are numerous challenges in undertaking studies in infants. These studies were started by PPI Sponsors years after the studies in older children were completed for several reasons:

- Lack of neonatal animal toxicity
- Lack of age-appropriate formulation or dosage form
- Lack of agreement on the scope and design of the studies
- Need to harmonize the PWR across several sponsors
- Lack of an available clinical end-point or PRO instrument

These background activities typically take longer than planned due to unexpected challenges. It is advisable to begin early.

Conducting studies in infants is also difficult because it is deemed a fragile population and additional safe-guards are required. Independent Review Boards/Independent Ethics

Committees (IRB/IEC) are typically inexperienced with such studies and make it very difficult to obtain approval. Any deviation from local standard of practice is typically refused. In the infant studies, many sites refused to conduct pH-metry because it wasn't part of their routine practice. The efficacy study in infants was easier to enroll but the number of sites required was large with the number of subjects per site quite low. It was not unusual to target 50% more sites than likely needed because so many were never initiated or never enrolled. Many sites refused to participate because the effort to start the study was high and the number of potential subjects was too low to make it worthwhile in spite of added grants for the start up expense. Although, Protonix® is only licensed by Pfizer for the United States and the studies were requested by the FDA, these infant studies were not possible to conduct solely within the United States. This added more complexity since the standard of practice is not uniform worldwide. It would be helpful for future trials for the FDA to work with the European PDCO to harmonize requirements since endorsement of a clinical program by both agencies would make the conduct of a worldwide study more feasible.

There is generally poor acceptance by IRB/IECs, investigators and parents of placebo-controlled trials in pediatric patients. This severely limits potential study designs and often leads to small uncontrolled studies that are difficult to interpret. This was one of the main drivers for the treatment-withdrawal design because it limited the exposure to placebo. Clearly comparator studies, when feasible, are preferred for this population. Alternatively, where standard of care is providing some benefit, adding on to standard of care may be feasible with a placebo-controlled trial.

It was also difficult to find investigators with the interest and experience in conducting any clinical trials. As a result, considerable investment on the part of the sponsor was required to train and develop pediatric investigators as part of the conduct of the Pediatric Written Request. It was, however, very rewarding to watch the development of investigators and sites over time. It would be helpful if the FDA worked with the Academy of Pediatrics to encourage training of potential investigators.

In general, many sponsors are reluctant to begin pediatric programs until a drug is approved and marketed for adults. In addition, few anticipate the challenges and time involved in conducting these studies. Benchmark data on timelines by disease area and age-group would be helpful for sponsors new to pediatric trials.

7.0 2010 PERSPECTIVE OF INFANT GERD

Gastroesophageal reflux disease (GERD) has been increasingly diagnosed in infants despite the challenge of distinguishing normal physiologic reflux from GERD in this young age group.[4,36,37,38,39,40,41,42] In the absence of a proven and safe pharmacological method to reduce transient lower esophageal sphincter relaxations, which allow the gastric contents to reflux up into the esophagus, pharmacologic treatments such as proton pump inhibitors (PPIs) aimed at reducing the acidity of the reflux are used.[43] The number of infants treated empirically with PPIs increased for many years despite limited published data and evidence-based treatment guidelines on the use of PPIs in infants.[37,38,40,4445,46,47] In the year 2000, the Children's Digestive Health and Nutrition Foundation (CDHNF) and the NASPGHAN organized a meeting in Washington, DC with the US FDA and members of industry and academia to discuss questions related to issues regarding the conduct of future pediatric trials in reflux disease.[44] The widespread empirical (off-label) use of PPIs in pediatric populations and calls for the evaluation of PPI efficacy and safety in large, randomized, controlled trials in these populations led the US FDA to request manufacturers of PPIs to conduct a battery of studies in adolescents, children, and infants, including neonates and premature infants.[46,48] The FDA made this request by way of a formal Pediatric Written Request (PWR). The major study design components, including the main inclusion criteria, were set forth by the FDA. In the battery of tests were efficacy, pharmacokinetic, and pharmacodynamic studies. Details of the study designs in the PWR underwent several updates since Dec 2001, and Wyeth Pharmaceuticals, the manufacturer of pantoprazole, received the final updated request for pantoprazole pediatric studies from the FDA in 2007. Data collection for the pantoprazole infant efficacy study (study 329) was completed in Nov 2007. Wyeth Pharmaceuticals submitted the results of all of the studies in the PWR to the FDA in November 2008. Results from studies of various available PPIs have now been reported for various pediatric age groups, including infants aged <1 year.[6,8,15,16,17,18,19] With the accumulated body of new research on PPIs, as well as new information regarding diagnostic technologies, the general thinking regarding diagnosis and treatment in infants has evolved since the time the PWR was first issued in Dec 2001 and even since the last update received by Wyeth Pharmaceuticals in 2007.[1,36]

Pantoprazole and other PPIs have proven to be efficacious in pediatric populations aged 1 year and older; however, studies conducted using four different PPIs (pantoprazole, esomeprazole, lansoprazole, omeprazole) and various study designs have all failed to show symptoms improvement in infants.[8,19,49,50] The newly revised 2009 NASPGHAN guidelines by Vandenplas et al do not recommend that PPIs be used in infants, citing 3 double-blind, placebo-controlled

studies in infants or preterm infants conducted with omeprazole or lansoprazole that failed to show a drug effect on symptoms.[6,19,36,50] The reason suspected by Vandenplas et al for the failure of those three studies is a mistaken diagnosis of GERD: 'no placebo-controlled treatment trial, in which enrollment was based on ''typical'' GERD symptoms, has demonstrated symptom improvement in infants. This result may be because of a lack of specificity of symptom-based diagnosis of GERD, especially with esophagitis, in this age group. Double-blind randomized placebo-controlled trials show that PPI therapy is not beneficial for the treatment of infants with symptoms that previously were purported but not proven to be due to GERD'.[36]

Given the failure of these various infant studies, the design, conduct, and results of the studies warrant further discussion. The pantoprazole infant efficacy study was designed such that after a 4-week open-label period of treatment with pantoprazole, patients received conservative therapy with either pantoprazole or placebo in a double-blind fashion for an additional 4 weeks.[8] If the rate of withdrawal due to lack of efficacy was found to be lower in the pantoprazole group during this double-blind period, it would indicate efficacy over placebo. The weekly GERD symptom score (WGSS) showed significant cumulative improvement each week during the open-label period and, unexpectedly, also throughout the 4-week double-blind period when half of the patients were switched to placebo, indicating that the treatment improvments attained during the open-label period were maintained during the double-blind period for all patients, regardless of whether they were switched to placebo or maintained on pantoprazole (Figure 5-3). Consequently, the withdrawal rates due to lack of efficacy in the double-blind period were low in both groups and nearly identical (11.5% pantoprazole, 11.2% placebo), and it could not be concluded that pantoprazole plus conservative therapy had efficacy over placebo plus conservative therapy using this treatment-withdrawal design. However, given this study design, it was impossible to determine the role of pantoprazole, if any, in the symptom improvement demonstrated during the open-label treatment period.

The difficulties encountered in the study, including the limitations of the study design, suggestions for improvement, and the results of the withdrawal period are discussed further below.

7.1 Limitations of the 3001B3-329-WW Study Design

The study design had several limitations, some of which appear more evident in retrospect.

7.1.1 Age Issues and the Treatment-Withdrawal Design

The infant age group itself poses a challenge in the clinical trial setting. The mean age in study 329 was 5 months at baseline, a time when infants are approaching the second half of the first year when epidemiological studies typically show a decrease in the prevalence of GERD.[2] Up to 70% of healthy newborns and infants have physiologic regurgitation that generally improves spontaneously by age 12-14 months.[37] The prevalence of daily regurgitation in healthy infants peaks at 67% of infants at age 4 months, and decreases 61% at 6 months, 21% at age 7 months and 5% at age 10-12 months; the prevalence of regurgitation described as "a problem" by parents peaks at 23% of infants at age 6 months and decreases to 14% by age 7 months.[2] At 6 months of age infants begin to eat solid food, which decreases the volume of feedings. They also begin to spend more time in an upright posture. Omari et al reported a decrease in transient lower esophageal relaxations in older infants, possibly reflecting increased competence of the lower esophageal sphincter.[51]

Consistent with this concept that regurgitation spontaneously resolves in many infants as they mature, in study 329, patients older than 6 months at baseline had greater improvements in WGSS from baseline to the final week ($p<0.005$), suggesting that any potential benefit of drug plus conservative treatment could be masked by the effects of maturation.[8] Additionally, the older infants (>6 months) had numerically lower mean WGSS and GSQ-I scores at baseline than the younger infants, though the differences were not statistically significant, again suggesting maturation is a factor in GERD severity (data on file). Thus, in our infant efficacy study, it was not possible to differentiate between treatment effects and maturation effects.

While the treatment-withdrawal design had the benefit of limiting exposure to placebo, a parallel-group design would have overcome the confounding effect of maturation on symptom improvement. The parallel-group design would have also enabled more strict criteria for efficacy based upon symptom improvement rather than withdrawal rates, which could be influenced by parent and physician anxiety over the use of placebo. However, in study 329, stricter criteria regarding withdrawal due to lack of efficacy would not have altered the outcome of the study because the withdrawal rates were low in both groups, and there were no differences in withdrawal rates by any criteria (see Table 5-3).

The lansoprazole infant study did use a placebo-controlled parallel-group design to study the effect of treatment in infants with suspected GERD. The responder rate was identical in infants who received drug and those who received placebo after up to 4 weeks of treatment (54% in each group); however, the study had several limitations, including the use of a single symptom, meal-

related crying, as its efficacy endpoint.[19,52] Additionally, in the lansoprazole study, infants were given 7-14 days of non-standardized conservative (nonpharmacologic) treatment prior to randomization, but randomization qualification required that the conservative treatment failed to decrease meal-related crying to <25% of all feedings during the final 4 pretreatment days, meaning that infants were given only 3-10 days to improve on conservative treatment before they were assessed for randomization.[19] Conservative therapy was not continued in any organized fashion throughout the study. Also, the lansoprazole study collected only meal-related crying data; however, the feedings themselves would have provided a buffering effect on gastric acid, and could render moot the acid-lowering effect of the PPI drug. It has been found by pH-impedance monitoring, that the proportion of non-acid reflux events in infants is 61% during the first hour after a meal, decreasing to 39% between the first and second postprandial hours and to 29% at >2 hours postprandial.[53] Additionally, the lansoprazole study allowed subjects to drop out after the first week and receive open-label treatment. Forty percent of subjects dropped out early, which undermined the study considerably.

7.1.2 Diagnosis and Patient Selection

An important aspect of study design is the ability to enroll the correct patient population, ie, patients with GERD, and exclude infants with physiologic GER; however, there is much overlap of symptoms in GERD and GER. A study with only patients with GERD may have been more likely to demonstrate efficacy with a treatment-withdrawal study design. The most recent definition of GERD in infants published in 2009 is "a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications".[37] In a global consensus of pediatric GERD, the paper reports that the symptom-based diagnosis of GERD in infants "remains a problem" but offered no immediate solution.[37] Reliance on symptoms alone makes the diagnosis difficult because other disorders such as eosinophilic esophagitis, cow's milk allergy, and infantile colic have symptoms that overlap with those of GERD.

In study 329, a multi-pronged approach was used to identify and exclude infants without GERD. The inclusion criteria aimed at selecting infants with GERD from a pool of infants with predominantly a clinical diagnosis of GERD were a modified GSQ-I score of >16 at both screening and baseline after 2 weeks of comprehensive standardized conservative therapy. The original GSQ-I is validated to differentiate between healthy infants and those with GERD, though not between those with GERD and those with GER.[21]

To exclude infants who would benefit from non-pharmacologic therapy, standardized conservative therapy was provided for 2 full weeks during screening (smaller more frequent

feeding with sponsor-provided hypoallergenic formula thickened with rice cereal for non-breast-fed infants, and general instructions about GERD, including positioning and environmental exposure). Cow's milk allergy was not specifically tested, but the use of hypoallergenic formula may have addressed this. Study 329 also provided calcium-containing rescue antacids during screening and throughout the study for GERD symptoms lasting more than 5 minutes.

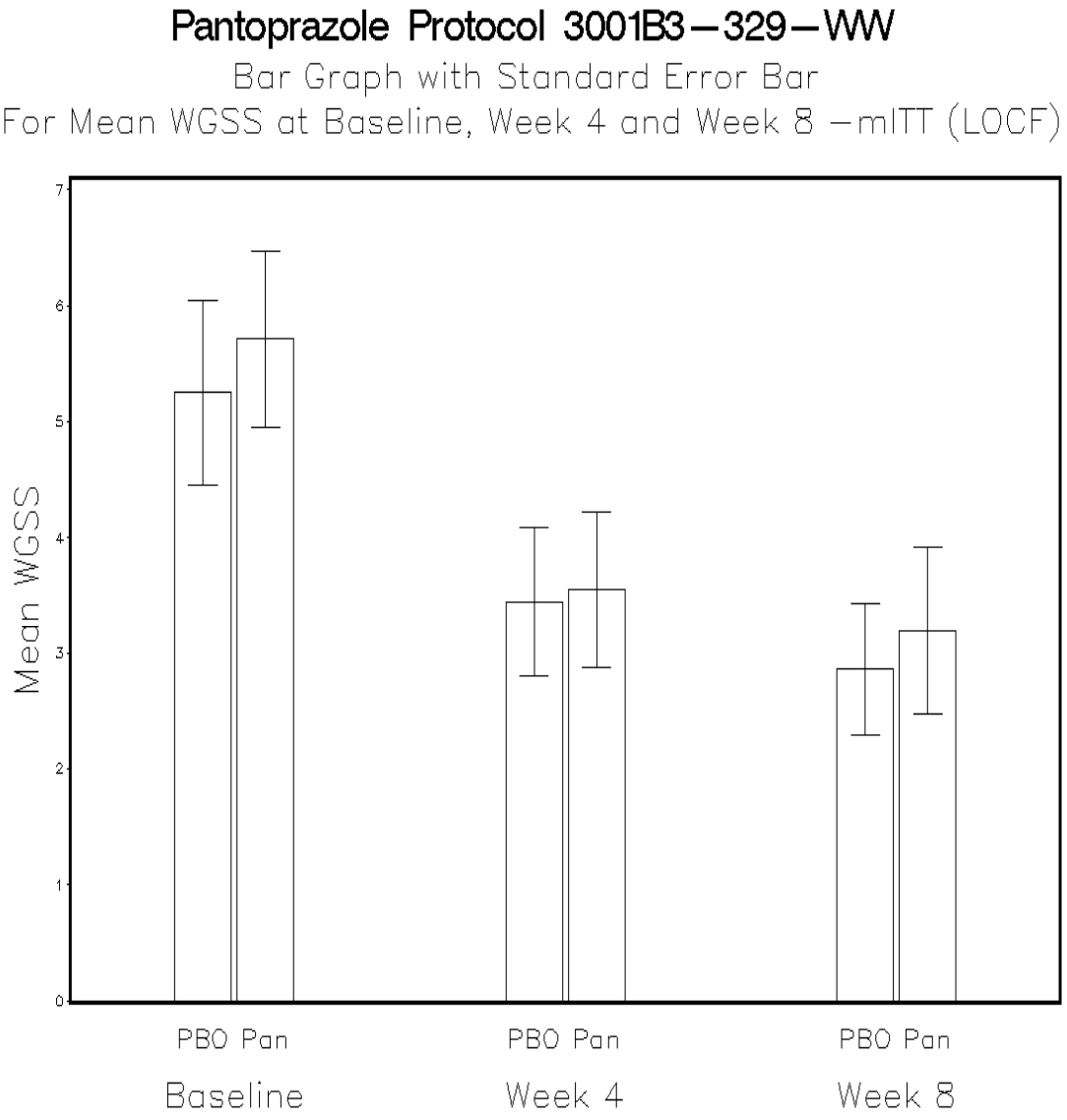
At the end of the screening period, only 5 (3.2%) of the 154 infants were excluded for the reason of improved GSQ-I scores. This contrasts with an exclusion rate of 24% reported from the screening of 2 studies conducted in patients referred from a primary pediatrician setting.[30,54] Patients in study 329 were recruited from pediatric gastroenterologists' offices with few from the primary care setting. The conservative measures were very similar in these studies. The main difference between study 329 and the more recent of the other two studies was the use of the GSQ-I vs the I-GERQ-R to assess symptom improvement.[54]

Among patients who did enter the study 329, those with higher (worse) GSQ-I scores at baseline had greater improvements in WGSS from baseline to the final week ($p<0.0001$). While raising the GSQ-I threshold would not have altered the results of this study, it is possible that in a parallel-design study, the ability to detect a difference from placebo would be greater if patients with less severe symptoms were excluded by raising the modified GSQ-I threshold score above >16 because there is less room for improvement if the infant enters the study with a lower symptom score.

Another question is whether or not specific symptoms are more or less responsible for the GSQ-I and WGSS scores. The 5 individual symptom frequencies were all weighted equally in the calculation of the WGSS (ie, no additional weighting multiplier was used) but the relative frequencies of the individual symptoms varied between patients. An investigation of the relative contributions of the 5 GERD symptom frequency components to the total changes of WGSS from baseline during the open-label phase is shown in Table 7-1 and Figure 5-4. All 5 components had their important shares of contributions to the total decrease in WGSS in each week, and the contributions were consistent during the 4-week open-label phase, though the contribution from "refusal to feed" decreased slightly from week 1 and continued to provide a smaller contribution than the other four components after week 1. Additionally, mean total WGSS significantly improved from baseline to week 4 in patients who were to receive pantoprazole or placebo during the double-blind withdrawal period, as well as from baseline to week 8 in patients who received pantoprazole or placebo (Figure 7-1). The populations of patients who eventually became two groups had comparable mean total WGSS at both baseline

and week 4 before half were switched to placebo, with no difference between groups at the end of the double-blind period (week 8) (see Figure 7-1).

Figure 7-1: Mean WGSS at Baseline, Week 4, and Week 8 in the Infants Who Eventually Received Pantoprazole or Placebo During the Double-Blind Withdrawal Period of Study 329



Footnote: Baseline and week 4 were based on treatment groups assigned in the DB phase. All subjects received Protoprazole during the 4—week OL run—in phase.

Program: /project/radnor/anarpt/production/pantop/p329/cb/programs/wgss_bar.sas
Output: /project/radnor/anarpt/production/pantop/p329/cb/output/wgss_bar.rtf

Table 7-1: Mean Changes in GERD Symptom Scores from Baseline and Percentage Contributions of Individual GERD Symptoms to WGSS Change During the Open-Label Phase: Study 3001B3-329-WW

Endpoint	Week 1 Mean (%)	Week 2 Mean (%)	Week 3 Mean (%)	Week 4 Mean (%)
WGSS	-0.58 (100.0)	-1.27 (100.0)	-1.71 (100.0)	-1.98 (100.0)
Vomiting/Regurgitation-1a	-0.10 (17.1)	-0.21 (16.2)	-0.38 (22.2)	-0.43 (21.8)
Irritability/Fussiness-2b	-0.14 (23.8)	-0.34 (26.9)	-0.40 (23.6)	-0.47 (23.6)
Choking/Gagging-3a	-0.12 (21.0)	-0.24 (19.2)	-0.34 (19.9)	-0.37 (18.5)
Arching Back-4a	-0.11 (19.2)	-0.30 (23.6)	-0.37 (21.4)	-0.46 (23.1)
Refusal to Feed-5ab	-0.11 (18.9)	-0.18 (14.2)	-0.22 (12.9)	-0.26 (13.1)

Source: *Program/project/radnor/anarpt/production/pantop/p329/cb/programs/pct_gerd.sas*

Endoscopy was not required in the PWR. This was fortunate because of the general resistance by parental and physicians regarding this procedure in infants. Diagnostic tests were previously performed in approximately a third of the patients who were enrolled in study 329. Patients were excluded if they had eosinophilic esophagitis that was either clinically suspected or confirmed by histology (≥15 eosinophils per high powered field). A total of 19.2% and 24.1% of the patients who eventually received pantoprazole and placebo, respectively, in the double-blind period had a diagnosis of GERD suggested or confirmed by previous diagnostic tests. Infants with eosinophilic esophagitis could not, therefore, be systematically excluded. One subject was diagnosed with eosinophilic esophagitis during the study and was withdrawn.

The infant pharmacokinetic and pharmacodynamic study (study 3001B3- 333-WW [333]) enrolled infants with a clinical diagnosis of GERD, which is a population similar to that screened for study 329. The 24-hour pH-metry results at baseline showed that approximately half of the infants had a reflux index <5% (normal), and although pantoprazole increased gastric pH, it did not change the already-normal esophageal pH or reflux index (see Table 3-2).[9] Enrollment of infants with an abnormal reflux index would have been required to demonstrate a difference in esophageal pH. A reflux index of >7%, considered abnormal according to the 2009 NASGPHAN guidelines, or even a higher threshold, such as >10%, could be used in combination with other tools to select for patients with more severe GERD.[36]

Salvatore et al evaluated the correlation between pH-metry and the presence of esophagitis at endoscopic biopsy.[55] In patients with a reflux index <5% or 10%, 74% and 71% respectively had normal histology indicating a high negative predictive value. Therefore, a reflux index of <5% or < 10%) could be considered as a screening test for patients with GERD for clinical trials. Salvatore et al also noted a disconnect between pH-metry and histology and the I-GERQ symptom score.[55] Nevertheless, a number of symptoms were reported in >50% of patients, suggesting a refinement of the questions could possibly make a difference in the evaluation.

The 2009 NASPGHAN guidelines state that "although many tests have been used to diagnose GERD, few studies compare their utility. Importantly, it is not known whether tests can predict an individual patient's response to therapy. Tests are useful to document the presence of pathologic reflux or its complications to establish a causal relation between reflux and symptoms, to evaluate therapy, and to exclude other conditions. Because no test can address all of these questions, tests must be carefully selected according to the information sought, and the limitations of each test must be recognized".[36] However, regarding pH-metry and endoscopy, the guidelines also state that "Esophageal pH monitoring is useful for evaluating the efficacy of antisecretory therapy" and "Esophageal pH monitoring provides a quantitative measure of esophageal acid exposure with established normal ranges" but, "Abnormal esophageal pH monitoring has not been shown to correlate with symptom severity in infants." Similarly, since many histologic findings are non-specific, "Endoscopic biopsy is important to identify or rule out other causes of esophagitis, and to diagnose and monitor Barrett esophagus (BE) and its complications."

It may be that starting with symptoms was the wrong approach for selecting a population for evaluating the efficacy of a PPI. It may be that the role of pH-metry and endoscopy is to *exlude* patients who are unlikely to have acid reflux or who have other possibly confounding conditions, leaving a population of infants who have symptoms that need to be further characterized. Perhaps examination of the symptoms in the populations with an abnormal reflux index and histology using the GSQ-I or WGSS or other newer symptom evaluation tools would be useful.

7.1.3 Nature of Reflux in Infants

A study conducted in preterm infants and term neonates who received esomeprazole addressed the effect of PPI treatment on reflux volume as well as acidity via pH-impedance monitoring.[15] The pH-impedance testing allowed characterization of bolus reflux episodes as either liquid, gas, or mixed, and as either acidic, weakly acidic, alkaline, or weakly alkaline. Patients had GERD symptoms and a reflux index >5% prior to 7 days of treatment. Treatment significantly

improved reflux index as well as all other pH-based assessments of acid reflux. As would be expected, among the many pH-impedance-based assessments, treatment significantly improved only the number of acidic reflux events and the mean clearance time of acidic reflux; however, impedance testing misses detecting 59% of acidic reflux events that are detected by pH-metry in neonates.[56] In another pH-impedance study conducted in 34 infants (median age 7 months) who were referred for symptoms of GER, 47% of reflux events were characterized as acidic and 53% as nonacidic, and the proximal height of a reflux, regardless of character content, was predictive for symptoms of fussiness/pain, arching, and burping.[53] Although that study was conducted in infants with GER and not necessarily GERD, the failure of the PPI efficacy studies to show a drug effect on symptoms in infants could possibly be attributed to a lack of effect on the number of total bolus or non-acid reflux events, for which PPIs would never have any effect. It also highlights the importance of conservative therapy to reduce the total number of reflux events by way of smaller and more frequent feedings.

7.1.4 Dosing

It is possible that greater efficacy could be achieved not only by screening infants based upon pH-metry but also by increasing the dose of PPI or dosing frequency based upon pH-metry results until optimal results were achieved, as was observed in an omeprazole study.[57]

7.1.5 Clinical Endpoint Selection

The primary endpoint in the treatment-withdrawal design was withdrawal due to lack of efficacy. The parents and investigators were anxious regarding the switch to placebo. It is possible that over-reporting of symptoms could have led to inappropriate withdrawal. There appeared to be some separation between the pantoprazole and placebo groups in symptoms at week 5 (Figure 5-3). If symptom differences rather than withdrawal rates were chosen as the primary endpoint, it is possible that a difference could have been demonstrated at week 5, but a much larger sample size would have been required to demonstrate statistical significance. For 80% power, approximately 165 subjects per arm would have been required to detect a difference of 0.71, assuming a common standard deviation of 2.26 at the 0.05 significance level.

7.2 Possible Reasons for Lack of Relapse in the Placebo Group

Relapse was expected to occur in approximately 27% of patients in the placebo group in the withdrawal period based upon a famotidine study,[58] but the observed withdrawal rate due to lack of efficacy was approximately 11% in both treatment groups. The anticipated rebound in gastric acid secretion after stopping the PPI may not have occurred. The symptom improvements

attained during open-label treatment were maintained during the withdrawal period in both treatment groups. This could be due to maturation. It is important to recognize that infants typically improve in the second 6 months of life with the introduction of solid food, increased development of the lower esophageal sphincter, and greater time spent upright.

There may also have been an effect of the conservative (nonpharmacologic) measures that were applied from screening through week 8 in all infants. The 2001 pediatric reflux clinical practice guidelines did not specify the duration of a trial of conservative treatment, except for 1-2 weeks for a trial of hypoallergenic formula in formula-fed infants with vomiting.[4] The 2009 guidelines state that in infants with cow's milk protein allergy, vomiting frequency usually decreases within 2 weeks of eliminating cow's milk protein, and that in formula-fed infants with bothersome regurgitation and vomiting, extensively hydrolyzed formula or amino acid formula can be used for trials lasting up to 4 weeks.[36] (See Section 7.1.2, Diagnosis and Patient Selection)

It is possible that sufficient improvement occurred with pantoprazole and conservative therapy during the open-label phase such that conservative therapy plus rescue antacids were sufficient to prevent relapse. In adults, 64.0% of patients with erosive esophagitis have healing after 4 weeks of treatment with pantoprazole 40 mg/day.[59] Thus, it is conceivable that in study 329, healing of the acid-induced injury occurred, resulting in a prolonged treatment effect.

Another possible reason for the lack of relapse in study 329 is that post-PPI relapse may occur less rapidly in infants than in adults, especially given the high likelihood of non-erosive disease. Possibly the buffering effects of their frequent feedings aids the improvement. Four (4) weeks may have been too short a period to demonstrate a withdrawal effect.

8.0 SUMMARY AND CONCLUSIONS

Future PPI studies in infants need to select infants with more severe GERD and evaluate them with a parallel-group study design versus placebo or histamine-2 receptor antagonists (H2RA) plus conservative therapy. The current NASPGHAN guidelines are not helpful regarding patient selection for a clinical trial because troublesome symptoms are poorly defined. Downplaying the role of pH-metry and histology because of lack of correlation with symptoms may be premature. It may be that in a PPI clinical trial setting, they could play an important role in excluding patients without significant acid exposure or other diseases. However, because the guidelines de-emphasized the role of pH-metry and histology for the diagnosis of GERD, it may be nearly impossible to conduct a clinical study using such diagnostic tools.

A screening period with extensive conservative therapy was successful in excluding 24% of infants[30,54] in a primary care setting, but this was not helpful in distinguishing GER from GERD in a PPI clinical trial setting where patients were recruited from those referred to pediatric gastroenterologists, in that conservative therapy only excluded 3.2% of patients. Similarly, while the GSQ-I is effective in distinguishing infants with reflux symptoms from healthy infants, it is unclear whether it can separate GER from GERD at the current threshold of >16. Additional studies would need to be conducted to determine whether a higher threshold would be more effective in distinguishing the two populations. Additionally, symptom tools and conservative measures do not definitively exclude cow's milk allergy, eosinophilic esophagitis, or infantile colic, all of which have symptoms that mimic GERD.

Symptom evaluation tools could be improved via efforts to build on the tools currently available, including the GSQ-I and related e-Diary among others. Efforts to further define the GERD patient population based upon pH-metry and histology may be useful. The reflux index has a high negative predictive value. Screening patients to be considered for pharmacologic treatment based upon the reflux index and further refinement of patient selection based upon significant GERD symptoms may help define the GERD population most likely to benefit from PPI treatment. It may be that previous studies failed to demonstrate correlations because of the specific symptoms selected. Another population of potential interest is the infant with severe GERD under consideration for surgery. They would be most amenable to more comprehensive testing (pH-metry and possibly endoscopy) and a trial of PPIs would be appropriate prior to surgery. Using pH-metry to assess the dose might also be helpful in this population.

9.0 ATTACHMENTS

9.1 GSQ-I Questionnaire

3001B3-329-WW

GERD SYMPTOM QUESTIONNAIRE FOR INFANTS AGES1 THROUGH 11 MONTHS (GSQ-I)

Site No.	Patient No.	Patient Initials ☐☐☐	Visit ID		

Date Completed ☐☐ ☐☐☐ ☐☐
D D M M M Y Y

Relationship to Patient
☐ Mother ☐ Step Mother ☐ Grandmother ☐ Guardian
☐ Father ☐ Step Father ☐ Grandfather ☐ Other, *specify* _____

SYMPTOMS	QUESTION A How many times did each symptom occur in the past 7 days? *(such as 0, 1, 2, 3, etc)*
1. **VOMITING / REGURGITATION** Throwing-up / swallowing food, or liquids that have come back up into the infant's mouth.	☐☐ Times in the past 7 days **(Do not leave blank)**
2. **CHOKING / GAGGING**	☐☐ Times in the past 7 days **(Do not leave blank)**
3. **ARCHING BACK**	☐☐ Times in the past 7 days **(Do not leave blank)**
4. **IRRITABILITY / FUSSINESS** Episodes of crying during feeding or inconsolable.	☐☐ Times in the past 7 days **(Do not leave blank)**
5. **REFUSAL TO FEED**	☐☐ Times in the past 7 days **(Do not leave blank)**
TOTAL	☐☐ **Total should be > 16**

9.2 329 Diary Script

329 Diary Script **Final Approved GMC version 5.1**
09 Aug 2005

The questions in this diary are designed to collect information on your baby's symptoms of Gastroesophageal Reflux Disease since last evening. Please take the time to read and answer each question carefully. The same person should complete the diary each day.

Answer as completely as possible. If your baby was in child-care or with other caregivers, please ask them to give you the appropriate information.

Please complete the diary every evening at approximately the same time. For each question, please select the answer that best describes your baby **since last evening**. Note that "spit up and regurgitate" refer to anything coming into or out of the mouth.

1. Vomiting / Regurgitation

1a. Since last evening, how many times did the baby spit up (anything coming into or out of the mouth)?

1 ☐ None [GO TO QUESTION 2a]
2 ☐ 1 to 3 times [GO TO QUESTION 1b]
3 ☐ 4 to 6 times [GO TO QUESTION 1b]
4 ☐ More than 6 times [GO TO QUESTION 1b]

1b. Since last evening, how much did the baby *usually* spit up (anything coming into or out of the mouth)?

1 ☐ Less than 1 tablespoon
2 ☐ 1 tablespoon to 2 fluid ounces
3 ☐ More than 2 fluid ounces to half the feed
4 ☐ More than half the feed

[PROGRAMMER NOTE: ALL RESPONSES GO TO QUESTION 1c]

1c. Since last evening, did spitting up (anything coming into or out of the mouth) seem uncomfortable (i.e., crying, fussing, irritability) for the baby?

1 ☐ Yes
2 ☐ No

[PROGRAMMER NOTE: ALL RESPONSES GO TO QUESTION 2a]

2. Irritability / Fussiness

2a. Since last evening, did the baby cry or fuss during or after feedings?

1 ☐ Yes [GO TO QUESTION 2b]
2 ☐ No [GO TO QUESTION 3a]

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329 Diary Script **Final Approved GMC version 5.1**
09 Aug 2005

2b. Since last evening, how many times did the baby either cry a lot during or within 1 hour after a feeding?

1 ☐ None
2 ☐ 1 to 3 times
3 ☐ 4 to 6 times
4 ☐ More than 6 times

[PROGRAMMER NOTE: ALL RESPONSES GO TO QUESTION 2c]

2c Since last evening, how much of the time did the baby cry or fuss?

1 ☐ Less than 10 minutes
2 ☐ 10 minutes to 1 hour
3 ☐ More than 1 hour but less than 3 hours
4 ☐ 3 or more hours
5 ☐ All of the time

[PROGRAMMER NOTE: ALL RESPONSES GO TO QUESTION 3a]

3. Choking / Gagging

3a. Since last evening, during how many feedings did the baby choke or gag?

1 ☐ None
2 ☐ A few
3 ☐ About half
4 ☐ All or almost all

[PROGRAMMER NOTE: ALL RESPONSES GO TO QUESTION 4a]

4. Arching back

4a. Since last evening, how many times did the baby have episodes of arching back?

1 ☐ None
2 ☐ 1 to 3 times
3 ☐ 4 to 6 times
4 ☐ More than 6 times

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[PROGRAMMER NOTE: ALL RESPONSES GO TO QUESTION 5a]

5. Refusal to feed

5a. Since last evening, how many times did the baby refuse feedings even when hungry?

1 ☐ None
2 ☐ 1 to 3 times
3 ☐ 4 to 6 times
4 ☐ More than 6 times

[PROGRAMMER NOTE: ALL RESPONSES GO TO QUESTION 5b]

5b. Since last evening, how many times did the baby stop eating even when hungry?

1 ☐ None
2 ☐ 1 to 3 times
3 ☐ 4 to 6 times
4 ☐ More than 6 times

[PROGRAMMER NOTE: ALL RESPONSES GO TO QUESTION 6a]

6. Respiratory Symptoms

6a. Since last evening, did the baby have a cold or fever?

1 ☐ YES [GO TO QUESTION 6h]
2 ☐ NO [GO TO QUESTION 6b]

6b. Since last evening, did the baby have a cough *without a* cold?

1 ☐ YES [GO TO QUESTION 6c]
2 ☐ NO [GO TO QUESTION 6c]

6c. Since last evening, how much of the time did the baby have noisy breathing *without a* cold?

1 ☐ None of the time [GO TO QUESTION 6h]
2 ☐ A little of the time [GO TO QUESTION 6d]
3 ☐ About half of the time [GO TO QUESTION 6d]
4 ☐ All or almost all of the time [GO TO QUESTION 6d]

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6d. Since last evening, did the baby have noisy breathing when breathing out?

1 ☐ YES [GO TO QUESTION 6e]
2 ☐ NO [GO TO QUESTION 6f]

6e. Since last evening, did the baby's breathing have a wheezy or whistling sound?

1 ☐ YES [GO TO QUESTION 6f]
2 ☐ NO [GO TO QUESTION 6f]

6f. Since last evening, did the baby have noisy breathing when breathing in?

1 ☐ YES [GO TO QUESTION 6g]
2 ☐ NO [GO TO QUESTION 6h]

6g. Since last evening, did the baby's breathing have a croupy or barky sound?

1 ☐ YES [GO TO QUESTION 6h]
2 ☐ NO [GO TO QUESTION 6h]

6h. Since last evening, did the baby stop breathing or turn blue or purple?

1 ☐ YES [GO TO END]
2 ☐ NO [GO TO END]

Thank you for completing the diary today.

9.3 Table of Abbreviations

Abbreviations	Definition
AE	Adverse Event
C_{max}	peak serum concentration
CSR	clinical study report
CSS	composite symptom scores
DB	double-blind
EE	erosive esophagitis
FDA	Food and Drug Administration
GASP-Q	GERD Assessment of Symptoms in Pediatrics Questionnaire
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GSQ-I	GERD Symptom Questionnaire for Infants
H_2RA	histamine-2 receptor antagonist
ISS	individual symptom score
ITT	intent-to-treat
LOCF	last observation carried forward
n	number of subjects
OL	open-label
PD	Pharmacodynamic
PK	pharmacokinetic
PO	orally, oral
PPI	proton pump inhibitor
Proton pump	H^+, K^+-ATPase, the gastric enzyme that acidifies gastric secretions by pumping H^+ ions into the gastric lumen.
PWR	Pediatric Written Request
SD	Standard deviation
SE	Standard error
US	United States
VFE	Valid-for-efficacy
WGSS	Weekly GERD Symptom Score
ZES	Zollinger-Ellison syndrome

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